Marine Pollution Bulletin 185 (2022) 114365

Contents lists available at ScienceDirect

Marine Pollution Bulletin

journal homepage: www.elsevier.com/locate/marpolbul

Review

Unraveling cellular and molecular mechanisms of acid stress tolerance and resistance in marine species: New frontiers in the study of adaptation to ocean acidification

Silvia Simonetti [a,b,*], Valerio Zupo [b], Maria Cristina Gambi [c], Till Luckenbach [d], Ilaria Corsi [a]

[a] Department of Physical, Earth and Environmental Sciences, University of Siena, via Mattioli, 4, 53100 Siena, Italy
[b] Stazione Zoologica Anton Dohrn, National Institute of Marine Biology, Ecology and Biotechnology, Dep.t of BluBioTech, Napoli, Italy
[c] National Institute of Oceanography and Applied Geophysics, OGS, Trieste, Italy
[d] Department Bioanalytical Ecotoxicology, Helmholtz Centre for Environmental Research (UFZ), Leipzig, Germany

ARTICLE INFO

Keywords:
Ocean acidification
Marine organisms
Acid stress tolerance and resistance
Cellular and molecular responses
ATP-binding cassette (ABC) transport proteins

ABSTRACT

Since the industrial revolution, fossil fuel combustion has led to a 30 %-increase of the atmospheric CO_2 concentration, also increasing the ocean partial CO_2 pressure. The consequent lowered surface seawater pH is termed ocean acidification (OA) and severely affects marine life on a global scale. Cellular and molecular responses of marine species to lowered seawater pH have been studied but information on the mechanisms driving the tolerance of adapted species to comparatively low seawater pH is limited. Such information may be obtained from species inhabiting sites with naturally low water pH that have evolved remarkable abilities to tolerate such conditions. This review gathers information on current knowledge about species naturally facing low water pH conditions and on cellular and molecular adaptive mechanisms enabling the species to survive under, and even benefit from, adverse pH conditions. Evidences derived from case studies on naturally acidified systems and on resistance mechanisms will guide predictions on the consequences of future adverse OA scenarios for marine biodiversity.

1. Ocean acidification: lessons from naturally acidified systems

Ocean acidification (OA) refers to the currently ongoing process of a decrease of the surface seawater pH, widely recognized as one of the most hazardous environmental threats to marine ecosystems that are associated with global change (Doney et al., 2009). This phenomenon is due to the emissions of anthropogenically produced carbon dioxide (CO_2) into the atmosphere from combustion of fossil fuels that had sharply increased during the industrial revolution and since then remained at a high level (Bindoff et al., 2019; Takahashi et al., 2014). In pre-industrial times, the atmospheric concentration of CO_2 varied within a range of 180–300 ppm, with 280 ppm on average but changes in atmospheric CO_2 levels markedly accelerated in the 20th century (Joos and Spahni, 2008). A recently recorded monthly average, 421 ppm CO_2 in the air, was 1.5-fold above the pre-industrial value (Mauna Loa, June 2022; https://www.esrl.noaa.gov/gmd/ccgg/trends/mlo.html). Since the beginning of the industrial revolution, the pH of the ocean surface worldwide dropped by approximately 0.1 pH units, from 8.21 to 8.10 (Brewer, 1997; Caldeira and Wickett, 2003; IPCC, 2014; Jiang et al., 2019; https://www.climate.gov/news-features/understanding-climate/climate-change-atmospheric-carbon-dioxide). According to current prediction models, this trend will continue at the same or an even higher rate until the end of the century (0.036–0.400 pH units by the year 2100) (Bindoff et al., 2019; Brewer, 1997; Caldeira and Wickett, 2003; Cao et al., 2007). At present, seawater pH is lowest in the equatorial regions, whereas pH is highest in subpolar and polar waters; the surface ocean pH decreases at a slower rate in areas with lower pH, resulting in more homogeneous global surface ocean pH with time (Jiang et al., 2019; Takahashi et al., 2014). The increase of the partial CO_2 pressure (pCO_2) in the atmosphere leads to a net air-to-sea flux of surplus gas that modulates the Earth system responses to climate change and causes shifts in seawater and carbonate chemistry (Bates et al., 2014). The ocean works as a giant sink for the anthropogenically emitted CO_2, absorbing 20–30 % of emitted CO_2 (Bindoff et al., 2019), equaling nearly

* Corresponding author at: Department of Physical, Earth and Environmental Sciences, University of Siena, via Mattioli, 4, 53100 Siena, Italy.
E-mail addresses: silvia.simonetti@student.unisi.it (S. Simonetti), vzupo@szn.it (V. Zupo), mgambi@ogs.it (M.C. Gambi), till.luckenbach@ufz.de (T. Luckenbach), ilaria.corsi@unisi.it (I. Corsi).

https://doi.org/10.1016/j.marpolbul.2022.114365
Received 7 September 2022; Received in revised form 8 November 2022; Accepted 11 November 2022
Available online 23 November 2022
0025-326X/© 2022 Elsevier Ltd. All rights reserved.

2.4 Gt of carbon per year (DeVries et al., 2019). CO_2 dissolved in seawater forms carbonic acid (H_2CO_3), which is unstable dissociating into hydrogen (H^+) and bicarbonate (HCO_3^-) ions and, at a lower rate, carbonate ions (CO_3^{2-}). The increased H^+ input is sufficient to strongly affect the water chemistry causing an acidification shift in the alkaline seawater (Brewer, 1997; Raven et al., 2005). Currently, the surface seawater pH ranges globally between 7.9 and 8.2 (Takahashi et al., 2014) and it naturally fluctuates due to variable solar irradiation (photosynthesis to respiration ratio) and temperatures changing seasonally and among latitudes (Kapsenberg and Cyronak, 2019). Moreover, regional– and habitat–scale processes, such as phytoplankton blooms, upwelling and/or changes in photosynthesis and respiration, can influence seawater pH (Kapsenberg and Cyronak, 2019).

Anthropogenic OA, leading to an increase of HCO_3^- and a decrease in CO_3^{2-} in the seawater, reduces the saturation state of calcium carbonate ($CaCO_3$) (Raven et al., 2005), perturbing calcification processes (Raven et al., 2005) in marine organisms with calcareous exoskeletons or shells (Agostini et al., 2018; Albright et al., 2010). Thus, affected taxa include calcareous red algae, foraminifera, coccolithophorids, aragonite-producing pteropods, hard corals, mollusks, serpulid polychaetes and echinoderms (as reviewed in Burns, 2008; Foo et al., 2018; González-Delgado and Hernández, 2018; Orr et al., 2005). In addition to perturbed calcification, the shifts in pH and carbonate chemistry in seawater also influence the chemistry of compounds, such as heavy metal speciation with effects on the metals' bioavailability and toxicity to marine organisms (Doney et al., 2009; Jin et al., 2021; Kibria et al., 2021; Landrigan et al., 2020; Zeng et al., 2015). OA-related changes in seawater pH also caused a drastic modification of interindividual chemical communications (Mutalipassi et al., 2020; Zupo and Viel, 2020), impair organism's feeding ability (Maibam et al., 2012), physiology (Mutalipassi et al., 2019) but also their defenses towards toxicants (Zupo et al., 2015) and predators (Maibam et al., 2015). Therefore, although changes in pH values appear subtle, OA has direct and indirect implications to marine life (Garrard et al., 2014). Here we aim to provide an overview on marine biota dealing with low water pH in their habitats and on the mechanisms marine species use to survive and/or benefit from such limiting environmental conditions. Furthermore, the advantages of current knowledge deriving from case studies on naturally acidified systems to unravel future marine biodiversity OA scenarios are discussed. In the first part, some general aspects related to different approaches to study OA (*in situ*, field studies and bench-scale researches) and to the effects of OA at higher hierarchical scales, such as species, population and communities, to reach a conceptual and factual bridge between molecules/cells and organisms/communities are provided. Further sections and in its sub-paragraphs, although not exhaustive, are aimed to highlight the major outcomes of studies concerning the effects of acidified conditions on marine life, many of which used a meta-analysis approach (Dupont et al., 2010; Harvey et al., 2013; Hendriks et al., 2010; Kroeker et al., 2010, 2013a). The final part of this section is dedicated to organisms able to tolerate naturally acidified environments (low-pH/high-pCO_2) and to their ability to cope with such peculiar acid-stress conditions. Finally, in order to unravel the resistance ability to acid stress, the documented role of ATP-binding cassette transport proteins (ABC) in selected single cell organisms able to cope with low water pHs is discussed as a potential area of investigation in predicting future marine biodiversity scenarios.

Certain marine ecosystems are naturally exposed to extremely high CO_2 concentrations due to unique hydrogeological and biological phenomena, such as for instance hydrothermal vents from submarine volcanism and nutrient upwelling (González-Delgado and Hernández, 2018; Santana-Casiano et al., 2016). In waters of the mentioned areas, the pCO_2 is higher than that commonly found in surface oceanic waters (150–530 μatm, Takahashi et al., 2014) and it is in the range that is predicted for oceanic surface waters for the year 2100 (500–1370 μatm, IPCC, 2014). However, the pCO_2 in seawater can be extremely high in certain areas, such as for instance at the volcanic CO_2 system of the Castello Aragonese in Ischia Island (Italy) where pCO_2 values above 20,800 μatm have been recorded (Hall-Spencer et al., 2008).

The current concerns on the impact of OA on marine species and communities underline the importance of investigating how they deal with and/or are affected by such low pHs in naturally acidified systems, such as CO_2 vents (Foo et al., 2018; Hall-Spencer et al., 2008; Hernández et al., 2016; Kroeker et al., 2013b). Such knowledge will help us to unravel future scenarios of increasing global OA and predict "winners" and "losers" among marine species and communities (Gambi et al., 2016; Saha et al., 2019). Naturally acidified marine systems show anomalies in CO_2 concentration in the water mostly due to subtidal volcanic activity resulting in gas emissions, known as vents, that are enriched in CO_2. Such marine volcanic vents are globally distributed and are found in the Mediterranean Sea (volcanic CO_2 vents at Ischia Island, Italy, Foo et al., 2018), the Atlantic and Pacific Oceans (subtropical reefs of "Las Cabras" Canary Island, Spain, Hernández et al., 2016 and the tropical coral reefs of Papua New Guinea, Fabricius et al., 2011, 2014; González-Delgado and Hernández, 2018), and in the Southern Ocean (caldera of the active volcano of Deception Island, Antarctica, Di Giglio et al., 2021). Other phenomena causing naturally acidified seawater conditions comprise (i) karstification, a process in which acidic waters leaked into karst terrain dissolve the limestone and then flow into the ocean (*e.g.*, lagoons in Caribbean Sea) (Crook et al., 2016), (ii) hydrographic-biological processes (*e.g.*, Palauan reef system) (Shamberger et al., 2014), (iii) upwelling of cold water rich in carbon (such as in the Arctic Ocean) (Chierici and Fransson, 2009). Those naturally acidified areas have become particularly relevant as open-lab scenarios to predict detrimental impacts of OA on natural populations and communities as for instance the disintegration of bivalve shells (Rodolfo-Metalpa et al., 2011) and changes in community structure (Barruffo et al., 2021; Crook et al., 2016; Esposito et al., 2022; Kroeker et al., 2013b; Vizzini et al., 2017).

2. Direct and indirect effects of OA on marine organisms

Changes in ocean chemistry can directly and indirectly affect marine ecosystems at several levels, from single species up to communities, leading to a fundamental change in their relationships including structures and functions of all ecosystems. Current knowledge on the impacts of low pH conditions on marine organisms has been obtained by studies conducted either *in situ* in natural acidified systems or on a bench-scale under controlled laboratory conditions including mesocosms to simulate natural OA scenarios. Bench-scale *in vivo* studies have addressed a wide range of autotrophs and heterotrophs species as well as time of exposure (from 20 min up to 12 months) (Zupo et al., 2015; Hennige et al., 2020) and with seawater pH lowered only by an input of CO_2, to simulate natural processes.

In situ studies on marine invertebrates mainly focused on polychaete species, which are considered useful indicators of community composition and excellent models to investigate individual mechanisms for acclimation and adaptation to OA (Calosi et al., 2013; Gambi et al., 2016; Ricevuto et al., 2014, 2015). Approximately 60.4 % of investigated species and related studies here reported belong to the class of Polychaeta. The remaining (39.6 %) is composed mainly by Malacostraca (26.1 %) and in a smaller percentage by Gastropoda (9.2 %), Anthozoa and Ophiuroidea (1.4 % each one), Bivalvia (1.0 %) and Echinoidea (0.5 %) (Fig. 1a, Table S1). Effects of acidified environments on plants and algae have also been studied, mainly focused on assemblages in *in situ* observations (Porzio et al., 2011; Vizzini et al., 2017).

Bench-scale studies using marine invertebrates include mainly mollusks (42.6 % of which 25.6 % gastropods and 17.0 % bivalves) due to their economic importance and their role as bioindicators for marine pollution (Goldberg et al., 1978; Shumway and Parsons, 2006) followed by Malacostraca (34.0 %), Polychaeta (12.8 %), Anthozoa (6.4 %), Hexanauplia and Echinoidea (each 2.1 %) (Fig. 1b, Table S1).

Polychaeta represent one of the most abundant groups of

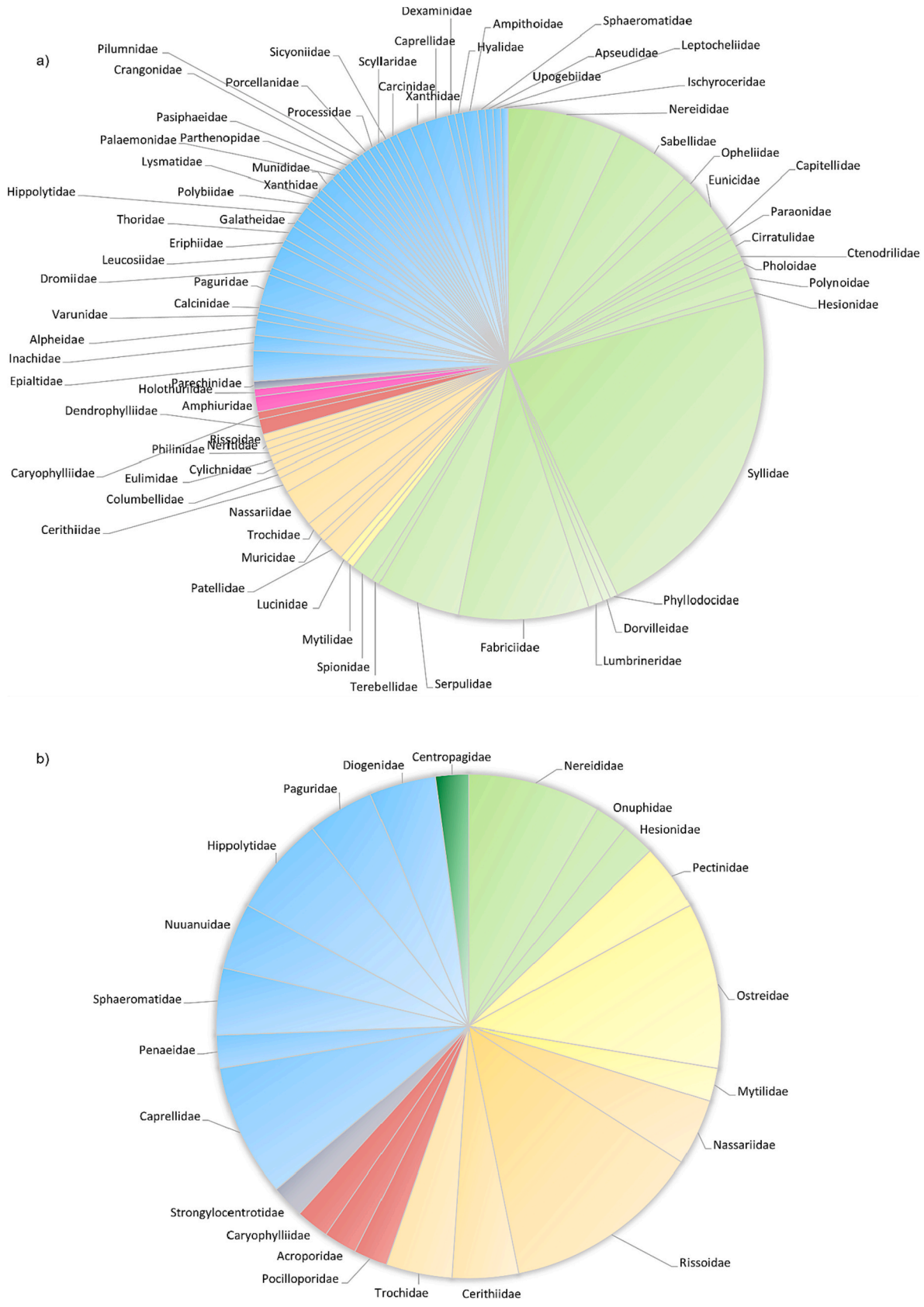

Fig. 1. Families of marine invertebrates investigated in OA effects studies *in situ* (a) and in bench-scale settings (b). Colors refer to: Polychaeta (light green), Bivalvia (yellow), Gastropoda (orange), Anthozoa (red), Ophiuroidea (pink), Echinoidea (dark blue), Malacostraca (light blue) and Hexanauplia (dark green). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

invertebrates within benthic communities and show high functional diversity (Jumars et al., 2015; Olsgard et al., 2003). Interestingly, they exhibit different tolerance to low-pH conditions depending on the taxa (Giangrande et al., 2014) and are considered excellent models to investigate effects of acidified environments (Calosi et al., 2013; Gambi et al., 2016; Ricevuto et al., 2014, 2015), being also abundantly in naturally acidified areas (Ricevuto et al., 2012; Vizzini et al., 2017). So, many studies on the effect of OA, mainly conducted *in situ*, have been focused on these organisms. Furthermore, since congeneric species can show opposite responses to acid stress, this group is a fascinating candidate to understand the mechanisms at the base of acclimation and adaptation to low-pH environments.

Mollusca are one of the most diverse groups of marine invertebrates and they are distributed ubiquitously. Acidified environments could represent a serious threat for them impacting calcifying processes and their presence is very reduced in natural low-pH/high-pCO_2 areas (Ricevuto et al., 2012). Since their great ecological and economic value (Ponder and Lindberg, 2008), mollusks have been largely investigated to understand their response when exposed to low pH scenarios.

2.1. Evidence for OA effects on population and community levels

Several studies at the population and community levels have been carried out to evaluate ecological consequences (shown in Fig. 2) of a lowered seawater pH. They clearly show that chronic exposure to elevated pCO_2/lowered pH levels cause changes in community structure, with a reduction in ecological diversity and trophic complexity (Fabricius et al., 2014; Gambi et al., 2016; Garrard et al., 2014; Hall-Spencer et al., 2008; Kroeker et al., 2013b; Teixidó et al., 2018; Vizzini et al., 2017). With a decrease in pH (pH range from 7.9 to 6.6), shifts in community composition and structure and loss of habitats have been reported (Hall-Spencer et al., 2008; Kroeker et al., 2013b, 2013c), including coral reefs worldwide (Albright et al., 2018; Fabricius et al., 2014; Hennige et al., 2020; Hoegh-Guldberg et al., 2007; Kelaher et al., 2022). Thus, habitats affected by OA lose their ability to support high biodiversity (*i.e.*, decreases in numbers of species and in the community structure complexity). A slight decrease in pH values (*i.e.*, reduction from 0.3 to >1 units) has been reported to cause alterations in inter-species balance with consequences on the population composition. Researchers have observed variations in settlement and recruitment dynamics of benthic communities and in competitive relationships between different invertebrate groups inhabiting naturally acidified environments (Crook et al., 2016; Kroeker et al., 2013b, 2013c; Ricevuto et al., 2012, 2014). Changes in interaction among organisms have also been shown in laboratory experiments (Maibam et al., 2015; Mutalipassi et al., 2019, 2022; Zupo et al., 2015). As a consequence, alterations in feeding habits may occur in these acidified environments (Maibam et al., 2015). Observed effects of a slightly lowered pH (7.7) were changes in the production of volatile organic compounds (VOCs) by algae (*Cocconeis scutellum* var. *parva*, *Diploneis sp.* and *Ulva prolifera*) upon exposure at these conditions for 16 days (Mutalipassi et al., 2022) and an altered odor sensing ability in the copepod *Centropages typicus* (Maibam et al., 2015). Thus, such modifications influence behavioral responses indirectly but can also impact community structure. Differences in epifaunal communities associated with seagrass *Posidonia oceanica* because of changes in attraction/repulsion reactions due to pH decreasing (from pH 8.1 to pH 7.7) have been documented (Zupo et al., 2015).

Generally, in low-pH environments, calcareous species (as the erect and crustose coralline algae, barnacles and calcareous tube worms) decrease in abundance when they enter in competition with fleshy algae (Kroeker et al., 2013c), and a connection between those changes and community depletion has been identified (Kroeker et al., 2013b, 2013c). High CO_2 levels (pCO_2 > 520 μatm) are associated with a reduction in the number of taxa (Fabricius et al., 2014; Gambi et al., 2016; Vizzini et al., 2017) and in a modification of relative abundance of species (Kroeker et al., 2013c) dictated by their different sensitivity towards low pH. Some taxa are able to tolerate very low pH levels (down to pH 6.6) (Calosi et al., 2013; Fabricius et al., 2014; Ricevuto et al., 2014) and result highly abundant in naturally acidified marine areas (the Ischia vents, Italy); those include the polychaetes *Amphiglena* spp., *Syllis prolifera*, *Platynereis cf. dumerilii*, *P. cf. massiliensis, Parafabricia mazzellae*, *Brifacia aragonensis* (Gambi et al., 2016; Giangrande et al., 2014;

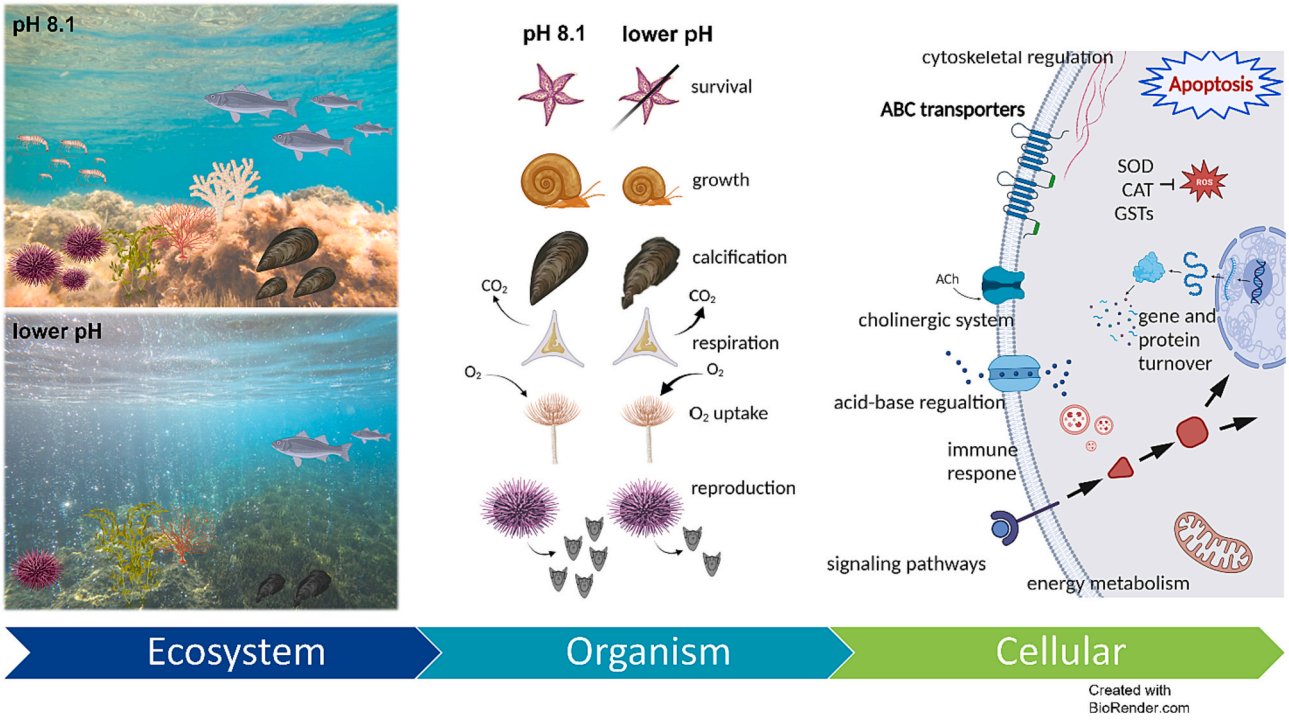

Fig. 2. Conceptual representation of effects of low-pH/high-CO_2 environment at different levels, from whole ecosystem communities down to single species and cellular affected pathways.

Ricevuto et al., 2014). However, the ability to adapt to OA is not ubiquitous in all species (Rastrick et al., 2018) and varies according to developmental stage (Kroeker et al., 2010) and/or reproductive traits (Gambi et al., 2016; Lucey et al., 2015). A widespread dominance of generalist species has been documented in naturally CO_2-enriched environments, as for instance at Ischia and Panarea vents (Esposito et al., 2022; Foo et al., 2018). More recent studies documented an abundance in primary producers (*e.g.*, algae), seagrasses (like *P. oceanica* and *Cymodocea nodosa*), herbivores and non-calcareous filter feeders, whereas carnivores and calcifying both fail (Gambi et al., 2016; Garrard et al., 2014; Hyun et al., 2020; Kroeker et al., 2013c; Vizzini et al., 2017). Calcifying species are the most impacted by OA triggering changes in water chemistry (Cigliano et al., 2010; Crook et al., 2016; Gambi et al., 2016; Kroeker et al., 2010; Ricevuto et al., 2012; Vizzini et al., 2017) and, only those employing less soluble forms of $CaCO_3$ are more resistant (Kroeker et al., 2010). Their reduction or even their disappearance has been documented in regions characterized by low pH. For instance, Hall-Spencer et al. (2008) reported a strong reduction in abundance of the sea urchins *Paracentrotus lividus* and *Arbacia lixula* at pH 7.4–7.5, while Vizzini et al. (2017) reported the absence of the mollusk bivalve *Lucinella divaricata* at sites with pH 7.96. Among primary producers, non-calcareous algal species are predominant while the calcifying ones disappear (Crook et al., 2016; Hall-Spencer et al., 2008; Kroeker et al., 2013b, 2013c). Observations of the community structure at various naturally rich CO_2 hydrothermal vents have highlighted differences in macrophyte composition between pH 8.1 and acidified sites (pH from 7.9 to 6.2) and disappearance of calcareous epiphytes in low-pH areas or even when pH decrease by 0.1 units (Hall-Spencer et al., 2008; Mecca et al., 2020; Porzio et al., 2011; Vizzini et al., 2017). The occurrence of malformation in calcareous coccolithophores (D'Amario et al., 2020) as well as shell corrosion in adult bivalves and gastropods (Duquette et al., 2017; Hall-Spencer et al., 2008; Rodolfo-Metalpa et al., 2011) has been reported to significantly intensify with an increase of pCO_2. Though some calcareous species are able to resist at acidified conditions thanks to their ability to protect their exoskeleton or shell from erosion as it is the case of the Mediterranean mussel *Mytilus galloprovincialis* and the zooxanthellate coral *Balanophyllia europaea* (Rodolfo-Metalpa et al., 2011). Furthermore, negative effects on species and taxa include a simplification of the structure of food webs (Vizzini et al., 2017) and a reduction of functional diversity (Kroeker et al., 2013b; Teixidó et al., 2018) which weak the whole ecosystem function and services (Zunino et al., 2019). Teixidó et al. (2018) reported a loss in functional entities (FEs, groups of species sharing the same trait values) associated to a lowering pH gradient (from 8.06 to 6.59 pH units) in the temperate benthic assemblages of the volcanic vents of the Castello Aragonese. In this environment, the majority of FEs are represented by a single species with a lack of functional redundancy. Furthermore, due to changes in community composition, a redistribution of species abundance can be found. These traits can bring from an increase in vulnerability of less plentiful FEs to new stressors and may lead to a reduction in the long-term resilience of the ecosystem which affect its ability to cope with further future environmental changes.

Moreover, it is worth mentioning the discovery of a few new species that have been described as primarily associated with shallow CO_2 vents systems, such as the Fabriciidae (Annelida, Sabellida) *Brifacia aragonensis* and *Parafabricia mazzellae*, and the sabellid *Amphiglena aenariensis* in the CO_2 vent system off the island of Ischia (Giangrande et al., 2014, 2021; Nilsson et al., 2011). Therefore, overall findings obtained from naturally acidified marine environments suggest that these systems, able to select morpho- and genotypes, can be used as "natural laboratories" to study also the evolutionary effects of OA. The evolutionary implications of OA for diversity and adaptation of the marine biota, highlighted by Sunday et al. (2011, 2013) remain, in fact, one of the main issues for future investigations on the far-reaching biological effects of one of the main aspects of the ocean's global climate change.

2.2. Individual scale evidence of OA

Biological responses to lowering seawater pH (summarized in Fig. 2) are species-specific and even phylogenetically close species can be differently affected (Gambi et al., 2016). Kroeker et al. (2010) have conducted a meta-analysis on biological responses to OA and revealed survival and calcification processes as the main targets, followed by growth and reproductive traits. As described above, few species can easily handle and survive in CO_2-enriched environments leading to a reduction in biodiversity, if they are not substituted. A reduction of calcification rates correlates to lower pHs in corals and in mollusks (Rodolfo-Metalpa et al., 2011). Moreover, $CaCO_3$ calcification process is slower in corals subjected to acidified conditions (Burns, 2008). Hyun et al. (2020) have shown opposite trends with proliferation of selected phytoplanktonic classes exposed to high pCO_2 levels based on sizes. Growth rates in smaller species are faster whereas higher-size species grow slowly. Besides, organisms living in acidified environments may exhibit lowered body sizes up to dwarfism (Calosi et al., 2013; Garilli et al., 2015). A further trait affected by low-pH conditions is body respiration; a reduction in cumulative respiration has been recorded in planktonic communities upon exposure to different CO_2 concentrations (240, 346, 348, 494, 868, 1075 and 1333 μatm CO_2) for 31 days in a mesocosm study (Spilling et al., 2016).

Organism's physiology is also affected by acidified conditions. Calosi et al. (2013) have shown a reduction in the uptake of oxygen (O_2) in polychaetes more sensitive to low pH compared to those more tolerant. Additionally, an increase in pCO_2 conditions by 817.68 μatm caused an increase in the heart rate of the caprellid amphipods *Caprella laeviuscula* and *Caprella mutica* (Lim and Harley, 2018).

Although OA is clearly posing a threat to natural marine life, some species can tolerate low seawater pH values either *via* acclimatization, as for instance *via* phenotypic plasticity or enhancement of basal antioxidant protection (Calosi et al., 2013; Ricevuto et al., 2015), or adaptation, through selection of the best genotypes (Calosi et al., 2013). Therefore, the understanding on how they adapt to such limiting conditions and the molecular/cellular bases of tolerance/resistance could unravel future biodiversity scenarios.

Different approaches have been used to unravel how organisms tolerate and/or resist to low pH starting from identifying pathways affected and the mechanisms involved at molecular to cellular levels (Fig. 2, Tables 1 and 2). To our knowledge, the major tools employed for this purpose are based on biochemical, transcriptomic and proteomic approaches.

Several studies have found changes in cellular and molecular processes to low-pH conditions (range 7.96–6.5) in mollusks, cnidarians, arthropods, echinoderms and worms, either upon acute (at least 3 h) and chronic (up to 60 days) exposures. However, even under similar exposure conditions, not always common expression patterns were found in selected pathways, as for instance in energy metabolism and signaling (as it can be seen in Tables 1, 2).

2.2.1. Cellular and molecular responses affecting the whole organism

Table 1 summarizes the main molecular pathways identified as targets and/or involved in low pH organisms' responses affecting the whole organism, as follows: metabolic pathways, calcification processes, cytoskeleton regulation, immune system and acid-base regulation described until now in various tissues/organs or whole organism.

Metabolism includes all the processes involved in the extraction of energy from the environment and making it available to the organism. Living organisms need a continuous supply of energy to survive and maintain all their internal biological processes. Homeostasis is supported by the coordination and complementarity of all the metabolic pathways in each cell (Wilson and Matschinsky, 2021) and a change in some of them could affect the whole organism. Alterations in energy metabolism induced by low-pH conditions were described in several marine invertebrates belonging to the phyla Cnidaria, Mollusca,

Table 1
Main pathways affected in marine invertebrates subjected to acidified water conditions. Responses at cellular and molecular level affecting the whole organism, both *in situ* and in the laboratory.

Species	*Situ*/ Lab	pH	Method	Response	Reference
Metabolic pathways					
Acropora millepora	*In vivo*	7.96 7.86	Transcriptomics	Down-regulation of 37 metabolic genes (29 of which are differentially expressed at higher acidic condition only)	Moya et al., 2012
Crassostrea gigas	*In vivo*	7.60	Proteomics	Down-regulation of protein involved in carbohydrate and lipid metabolism	Cao et al., 2018
Crassostrea hongkongensis (larvae)	*In vivo*	7.60 7.90 7.60	Proteomics	Down-regulation of enzymes involved in energy metabolism Up-regulation of several proteins involved in metabolism and energy production	Dineshram et al., 2013 Dineshram et al., 2015
Hediste diversicolor	*In vivo*	7.30 7.60	Biochemical analysis	Increasing in the metabolic rate, measured as electron transport system activity (oxygen consumption)	Freitas et al., 2016a
Litopenaeus vannamei	*In vivo*	7.00 7.20 7.40 7.60 7.80	Biochemical analysis	Higher levels of GOT and GPT	Muralisankar et al., 2021
Platynereis dumerilii	*In vivo*	7.80	Transcriptomics	Down-regulation of proteins involved in energy metabolism	Wäge et al., 2016
Pocillopora damicornis	*In vivo*	7.19 7.42 7.75	Transcriptomics	Up-regulation of genes related to energy production	Vidal-Dupiol et al., 2013
Paracentrotus lividus (immune cells)	*In situ*	7.80	Biochemical analysis	No differences in metabolic rate	Migliaccio et al., 2019
Paracentrotus lividus (immune cells)	*In situ*	7.80	Proteomics	Up-regulation of most enzymes involved in ammonium metabolism Various response of proteins involved in carbon metabolism, some enzymes were up-regulated and other were down-regulated Up-regulation of protein involved in pyruvate and propanoate metabolism	Migliaccio et al., 2019
Crassostrea hongkongensis (larvae)	*In vivo*	7.60 7.90	Proteomics	Either up- or down-regulation of proteins involved in general metabolism	Dineshram et al., 2013
Calcification/biomineralization and related processes					
Acropora millepora	*In vivo*	7.96 7.86	Transcriptomics	Complex effects, ion transporter proteins showed slight non-significant changes in transcription while carbonic anhydrases were down-regulated Similar number of genes encoding proteins of the skeletal organic matrix were up- or down-regulated	Moya et al., 2012
Crassostrea hongkongensis (larvae)	*In vivo*	7.60 7.90 7.60	Proteomics	Opposite effects on calmodulin depending on pH, down-regulation at pH 7.9 and slight up-regulation at pH 7.6 Up-regulation of calcification-related proteins	Dineshram et al., 2013 Dineshram et al., 2015
Pocillopora damicornis	*In vivo*	7.19 7.42 7.75	Transcriptomics	Up-regulation of genes involved in calcification at higher pH (7.75, 7.42) and down-regulation at the extreme level of pH (7.19) except for an extracellular CA that was up-regulated Up-regulation of genes encoding skeleton organic matrix proteins	Vidal-Dupiol et al., 2013
Cytoskeleton regulation					
Crassostrea gigas	*In vivo*	7.60	Proteomics	Up-regulation of proteins belonged to cytoskeleton regulation pathway	Cao et al., 2018
Crassostrea hongkongensis (larvae)	*In vivo*	7.60 7.90 7.60	Proteomics	Up-regulation of cytoskeletal proteins Either up- or down-regulation of proteins related to structure Down-regulation of proteins related to cytoskeletal functions	Dineshram et al., 2013 Dineshram et al., 2015
Platynereis dumerilii	*In vivo*	7.80	Transcriptomics	Up-regulation of proteins involved in cytoskeletal function	Wäge et al., 2016
Immune system					
Crassostrea gigas	*In vivo*	7.60	Proteomics	Down-regulation of proteins involved in immune response	Cao et al., 2018
Patinopecten yessoensis (mantle)	*In vivo*	6.50 7.50	Transcriptomics	Various regulation of genes involved in innate immune response; some genes were up-regulated at most time point whereas other were down-regulated	Zhu et al., 2020
Platynereis dumerilii	*In vivo*	7.80	Transcriptomics	Down-regulation of immune-related proteins	Wäge et al., 2016
Acid-base regulation					
Hediste diversicolor	*In vivo*	7.30 7.60	Biochemical analysis	Increasing activity of CA	Freitas et al., 2016a
Crassostrea gigas	*In vivo*	7.50	Transcriptomics	Up-regulation of CgsAC apart from in male gonad where is down-regulated	Wang et al., 2016

Abbreviations in the table: glutamic oxaloacetate transaminase (GOT); glutamic pyruvate transaminase (GPT); carbonic anhydrase (CA); soluble adenylyl cyclase (sAC).

Annelida, Arthropoda and Echinodermata. In the coral *Acropora millepora* a downregulation of metabolic genes upon an acute exposure of 3 days to pH 7.96 and 7.86 was observed (Moya et al., 2012). Suppression of energy metabolism was also found in the worm *P. dumerilii* (pH 7.8 for 7 d) (Wäge et al., 2016), in the Pacific oyster *Crassostrea gigas* (pH 7.6, 31 d) (Cao et al., 2018) and *Crassostrea hongkongensis* oyster larvae (pH 7.9 and 7.6 35d) (Dineshram et al., 2013). Interestingly, Dineshram et al. (2015) observed an opposite pattern for *C. hongkongensis* larvae after 19

Table 2
Main pathways affected in marine invertebrates subjected to acidified water conditions. Responses at cellular and molecular level affecting the cell integrity, both *in situ* and in the laboratory.

Species	*Situ*/ lab	pH	Method	Response	Reference
Oxidative status					
Crassostrea gigas	*In vivo*	7.6	Proteomics	Up-regulation of proteins involved in the oxidative response	Cao et al., 2018
Crassostrea hongkongensis (larvae)	*In vivo*	7.6	Proteomics	Up-regulation of proteins involved in cellular oxidative stress tolerance	Dineshram et al., 2015
Diopatra neapolitana	*In vivo*	7.1 7.3 7.5	Biomarkers	Increasing activity of antioxidant enzymes, in particular SOD was higher in polychaetes exposed to all low pH values compared to control, CAT activity increased in individuals exposed to pH values 7.3 and 7.1 and GSTs activity showed higher values only in organisms exposed to pH 7.3	Freitas et al., 2016b
Hediste diversicolor	*In vivo*	7.3 7.6	Biochemical analysis	Increasing activity of antioxidant enzymes, in particular SOD activity was higher in organisms exposed to pH 7.3, CAT activity showed no differences among individuals exposed to different pH and GSTs activity increased in polychaetes exposed to both pH values	Freitas et al., 2016a
Litopenaeus vannamei	*In vivo*	7.0 7.2 7.4 7.6 7.8	Biochemical analysis	Higher levels of SOD, CAT and LPO in shrimps exposed to all low pH values compared to control	Muralisankar et al., 2021
Platynereis spp.	*In situ*	7.8–6.6	Biomarkers	Oxidative status was not affected	Valvassori et al., 2019
Paracentrotus lividus	*In situ*	7.8	Proteomics Biochemical analysis	Higher TAC Enrichment of enzymes involved in oxidative processes and increase in immune defense activity	Migliaccio et al., 2019
Signaling pathway					
Crassostrea gigas	*In vivo*	7.5	Transcriptomics Biochemical analysis	Stimulation of $[HCO_3^-]$/CgsAC/cAMP signaling pathway	Wang et al., 2016
Crassostrea gigas	*In vivo*	7.6	Proteomics	Up-regulation of proteins involved in calcium signaling	Cao et al., 2018
Crassostrea gigas	*In vivo*	7.5	Transcriptomics	Stimulation of calcium signal pathways	Wang et al., 2020
Crassostrea hongkongensis (larvae)	*In vivo*	7.6	Proteomics	Down-regulation of signal transduction proteins	Dineshram et al., 2015
Pocillopora damicornis	*In vivo*	7.19 7.42 7.75	Transcriptomics	Down-regulation of genes involved in signal transduction	Vidal-Dupiol et al., 2013
Gene and protein turnover					
Crassostrea gigas	*In vivo*	7.6	Proteomics	Down-regulation of proteins involved in protein synthesis and degradation	Cao et al., 2018
Platynereis dumerilii	*In vivo*	7.8	Transcriptomics	Up-regulation of genes encoding proteins related to protein synthesis	Wäge et al., 2016
Paracentrotus lividus	*In situ*	7.8	Proteomics	Up-regulation of proteins involved in amino-acid degradation	Migliaccio et al., 2019
Platynereis dumerilii	*In vivo*	7.8	Transcriptomics	Up-regulation of genes encoding proteins involved in DNA replication processes	Wäge et al., 2016
Cholinergic function					
Patinopecten yessoensis	*In vivo*	6.5 7.5	Transcriptomics	Up-regulation of 7 *PyChEs* genes and down-regulation of the other 3 *PyChEs* genes; the different gene regulation seemed to be dependent on exposure time	Xing et al., 2021
Apoptosis					
Crassostrea gigas	*In vivo*	7.6	Proteomics	Up-regulation of proteins involved in apoptosis	Cao et al., 2018

Abbreviations in the table: superoxide dismutase (SOD); catalase (CAT); glutathione S-transferases (GSTs); lipid peroxidation (LPO); total antioxidant capacity (TAC); carbonic anhydrase (CA); cholinesterase (ChE).

days at pH 7.60. In response to acidified environments metabolic activity could be initially enhanced in order to facilitate homeostasis maintenance and avoid injuries while, beyond a certain exposure time, a rearrangement in energy allocation occurs and energy metabolism decreases (Freitas et al., 2016a). An increase in energetic metabolism in response to decreasing pHs was reported in the scleractinian coral *Pocillopora damicornis* after 21-d of exposure to pH 7.75, 7.42 and 7.19 (Vidal-Dupiol et al., 2013). Similarly, the polychaete *Hediste diversicolor* exhibited higher metabolic rate upon exposure to pH 7.6 and 7.3 for 28 days (Freitas et al., 2016a) as well as the shrimp *Litopenaeus vannamei* exposed for 7 weeks to 7.8, 7.6, 7.4, 7.2 and 7.0 (Muralisankar et al., 2021). While no differences in the metabolic rate occurred in the sea urchin *P. lividus* living in naturally acidified waters (pH 7.8) at the Castello vents of Ischia (Migliaccio et al., 2019). The modification of energetic metabolism in response to seawater acidification conditions suggests a shift in energy allocation in favor of other pathways. An

improvement in metabolism could indicate the use of energy reservoir to prevent cells from injuries (Freitas et al., 2016a) while it is possible that the reduction in the expression of metabolic genes could be a mechanism carried out by organisms to survive, by which energy would be channeled to more immediate stress responses (Dineshram et al., 2013; Moya et al., 2012). In Mollusca and Echinodermata other metabolic pathways were affected by exposure to acidified environments (pH range varies from 7.9 to 7.6). Increased expression of proteins involved in the metabolism of ammonium, pyruvate and propanoate were described in immune cells of specimens of the sea urchin *P. lividus* inhabiting naturally acidified sites (pH 7.8). In the same organisms a modulation of enzymes related to carbon metabolism occurred (Migliaccio et al., 2019). In *C. hongkongensis* larvae, proteins implicated in general metabolism resulted to be differentially expressed after 35 d of exposure to pH 7.9 and 7.6 (Dineshram et al., 2013).

Biomineralization processes provide organisms with a mineralized hard structure which protects them against external threats, like predators. Among these, calcification is the most common process and leads to the formation of calcium carbonate skeletals (Adey and Loveland, 2007). Biomineralization and calcification regulation is strictly related to the secretion of organic matrix molecules by the organisms being involved in mineral deposition (Falini et al., 2015). As described in paragraph 2.2, several studies identified negative effects on calcification processes due to OA (Kroeker et al., 2010; Rodolfo-Metalpa et al., 2011). Studies conducted on corals and bivalves also identified modifications in regulation of proteins related to calcification and biomineralization upon exposure to low-pH levels (ranging between 7.96 and 7.19). Different calcification-related proteins were investigated in these works, such as calmodulin, carbonic anhydrases (CAs) and transporters of calcium, bicarbonate and hydrogen ions. In specimens of *A. millepora* exposed for 3 days at pH 7.96 and 7.86, calcification was not affected by acidified conditions except for CAs which were found down-regulated. Furthermore, genes encoding proteins involved in skeletal organic matrix have been observed to be either up- or down-regulated (Moya et al., 2012). Down-regulation of gene encoding for proteins involved in calcification and biomineralization was observed in *C. hongkongensis* larvae maintained at pH 7.9 for 35 d while at lower pH (7.6) these proteins were slightly up-regulated (Dineshram et al., 2013). Similarly, an increase in calcification-associated proteins following low pH exposure (7.6) was reported in the same species (Dineshram et al., 2015). In the scleractinian coral *P. damicornis* exposed for 21 days to 3 different low pH values (7.75, 7.42 and 7.19), an up-regulation of genes encoding HCO_3^- transports, Ca_2^+ plasma membrane ATPase and CAs was found at higher pH (7.75 and 7.42) and a down-regulation was observed at the lowest (7.19) except for an extracellular CA that resulted up-regulated. In the same experiment, genes encoding proteins related to skeletal organic matrix appeared up-regulated (Vidal-Dupiol et al., 2013). Calcium homeostasis could be affected by acidified environments (Dineshram et al., 2013) altering calcification by influencing the central calcium signaling pathways (Moya et al., 2012). The enhancement of proteins involved in calcification and biomineralization has a key role in mitigate the impacts associated with acidified conditions (Dineshram et al., 2015; Vidal-Dupiol et al., 2013). Vidal-Dupiol et al. (2013) hypothesized that the upregulation of ion transporters could increase ion concentration leading to the maintenance of calcification efficiency or the aragonite saturation state in less favorable conditions. While a down-regulation in such genes causes decline in calcification rate. It is important to notice that calcification processes require a high amount of energy, therefore, if energetic metabolism is increased by low-pH also the calcification rate could improve (Dineshram et al., 2015; Vidal-Dupiol et al., 2013). Furthermore, down-expression of structural protein could suppress metabolism either at specific and general level (Moya et al., 2012), while induction of proteins related to skeleton formation and composition may sustain structural alterations and local changes in nucleation, cytosol growth inhibition and orientation (Dineshram et al., 2013; Vidal-Dupiol et al., 2013). The differences in response of skeleton proteins suggests a specific and unique role for each protein in mineral deposition which can lead to an enhancement of calcification in some sites and an inhibition in others (Moya et al., 2012).

Another pathway influenced by low pH exposure is cytoskeleton regulation. Cytoskeleton is a dynamic filamentous protein structure surrounding cells which has mechanical and structural functions, allows communication and exchanges with the external environment and is involved in cell division processes (Alberts et al., 2008). Alteration of the cytoskeletal architecture could affect cell stability and health and has been seen associated with some diseases, including neurological disorders (Muñoz-Lasso et al., 2020). Studies on Mollusca and Annelida described an increase in cytoskeleton protein expression upon low-pH exposure. Up-regulation of paramyosin and calponin was documented in the marine worm *P. dumerilii* upon exposure to pH 7.8 for 7 d (Wäge et al., 2016). Induction of proteins involved in cytoskeleton regulation were revealed in the pacific oyster *C. gigas* upon exposure to pH 7.6 for 31 d (Cao et al., 2018). Similarly, cytoskeletal proteins were up-regulated in *C. hongkongensis* larvae after 35 d of exposure to pH 7.9 and 7.6 (Dineshram et al., 2013) but not after 19 d (Dineshram et al., 2015). The increase in cytoskeletal protein production suggests a compensatory response to acidified environments that could cause positive cytoskeletal outcome (Cao et al., 2018; Dineshram et al., 2013).

The immune system is a network of numerous components and processes, which allows organisms to deal with diseases, infections and pathogens. It is fundamental for survival and its alterations could have tremendous consequences on health (Alberts et al., 2008). This system seems to be affected by low pH conditions (pH range 7.8–6.5) in either Mollusca or Annelida. A down-regulation of immune-related genes was documented in the polychaete *P. dumerilii* (pH 7.8, 7 d) (Wäge et al., 2016) and in the Pacific oyster *C. gigas* (pH 7.6, 31 d) (Cao et al., 2018). In the mantle of the Yesso scallop *Patinopecten yessoensis* 4 genes were modulated after 24 h of exposure to pH 7.5 and 6.5 (Zhu et al., 2020). In the short term the first proteomic response could be an enhancement of some immune proteins to activate defenses to cope with low pH but then, this process might imply a too elevated energy cost and thus be abolished. The suppression of proteins involved in immune responses may lead to a higher vulnerability to other stressors, such as pathogens, and to an impairment of the immune system (Cao et al., 2018).

Internal acid-base homeostasis maintains cellular and extracellular pH in the optimal range and is crucial to guarantee physiological functions in organisms. Acid-base balance was positively influenced by low pHs (7.6, 7.5 and 7.3) in Polychaeta and Bivalvia in long term experiments (16 and 28 days). Specimens of *H. diversicolor* exposed to pH 7.6 and 7.3 for 28 d showed an increased CA activity, which is involved in acid-base regulation in non-calcifying marine invertebrates (Freitas et al., 2016a). The same trend was observed in mRNA expression of *C. gigas*' soluble adenylyl cyclase (sAC), an oyster acid-base sensor, after 16 days to pH 7.5, except in male gonads where sAC was down-regulated (Wang et al., 2016). Acid-base regulation is essential for cellular homeostasis maintenance and an enhancement in this process could allow organisms to an increased metabolic capacity and to the preservation of cell acid-base balance (Freitas et al., 2016a). On the other hand, the decrease in sAC expression in oyster male gonads could endanger the fertilization process because sAC in oyster sperm is highly involved in maturation, motility regulation and the acrosome reaction.

2.2.2. Cellular and molecular responses affecting cell integrity

Table 2 summarizes the molecular and cellular mechanisms affecting cell integrity, such as: antioxidant response, signaling pathways, protein synthesis and degradation, DNA replication, cholinergic functions and apoptosis, described until now in various tissues/organs or whole organism.

Antioxidant activity prevents the potential negative effects of reactive molecules, such as reactive oxygen species (ROS), that are naturally produced during normal cell activity (Snezhkina et al., 2019). Stress conditions could result in a higher ROS production or a weakening

antioxidant response causing cell damage (Burton and Jauniaux, 2011). Low seawater pH (range 7.8–6.6) affected the oxidative status in Mollusca, Echinodermata, Arthropoda and Annelida by increasing antioxidant responses. This was documented in the oyster *C. gigas* (pH 7.6, 31 d) (Cao et al., 2018), in *C. hongkongensis* larvae (pH 7.6, 19 d) (Dineshram et al., 2015), in the shrimp L. *vannamei* (pH 7.8, 7.6, 7.4, 7.2 and 7.0, 49 d) (Muralisankar et al., 2021) and in immune cells of specimens of *P. lividus* inhabiting naturally acidified sites (pH 7.8) (Migliaccio et al., 2019). In the polychaetes *Diopatra neapolitana* and *H. diversicolor* antioxidant enzymes activity responded differentially to pH (pH range 7.6–7.1, 28 days). In *D. neapolitana* superoxide dismutase (SOD) activity increased at all pH levels while catalase (CAT) only at two lower pH (7.3 and 7.1) and glutathione S-transferases (GSTs) at pH 7.3 (Freitas et al., 2016b). In *H. diversicolor* SOD activity increased at pH 7.3 while no changes were observed at pH 7.6, CAT activity was not altered while GSTs increased at both pHs (Freitas et al., 2016b). Limited changes in oxidative status in *Platynereis* spp. upon exposure to low pH conditions were reported (Valvassori et al., 2019). Since SOD, GST and CAT are the major antioxidant enzymes preventing oxidative damage (Halliwell, 1974), the enrichment on these enzymes can be considered a defense mechanism put in place by organisms to prevent and protect themselves from cellular damage caused by ROS.

Signaling pathway represents the way to communicate between cells and consists in a sequence of cascade chemical reactions which control cell function. It is activated by an external molecule which binds to a cellular receptor initiating the communication (Alberts et al., 2008). Some of these processes were affected by low-pH conditions (pH 7.8–7.2) in Mollusca and Cnidaria. In the scleractinian coral *P. damicornis* genes involved in signal transduction resulted down-regulated at lower pH (7.42 and 7.19) while up-regulated at higher values (7.75) upon exposure for 21 d (Vidal-Dupiol et al., 2013). Larvae of the pacific oyster *C. hongkongensis* displayed a decrease in signal transduction proteins at pH 7.6 in 19 d (Dineshram et al., 2015). In the oyster *C. gigas* various signaling pathways were enriched by CO_2 exposure. The $[HCO_3^-]$/CgsAC/cAMP signaling pathway was stimulated by a 16-d exposure to pH 7.5 (Wang et al., 2016) and the calcium signaling pathway increased at pH 7.5 and 7.6 at different time points (7, 31 and 60 days) (Cao et al., 2018; Wang et al., 2020). Depending on the modified signaling pathway and life stage different effects could be expected. As for instance, the decrease in neuroglian expression in pacific oyster larvae exposed to pH 7.6 could lead to an abnormal neuronal development (Dineshram et al., 2015). Quite the opposite, the increase in calcium signaling pathway detected in *C. gigas* could play an essential role in homeostasis maintenance and its ability to deal with environmental CO_2 fluctuations (Wang et al., 2020).

The amount of protein inside cells is maintained constant over time by balancing their synthesis and degradation. This continuous turnover is regulated by the cells and depends also on their division cycle (Alber and Suter, 2019). During cell division, a crucial role is played by DNA replication which has to guarantee the correct genetic information transfer on the daughter cells (Alberts et al., 2008). Both protein synthesis and degradation and DNA replication were affected by low pH (7.6–7.8) in mollusks, polychaetes and sea urchins (Cao et al., 2018; Migliaccio et al., 2019; Wäge et al., 2016). The oyster *C. gigas* exposed for 31 d at pH 7.6 showed a down-regulation of proteins involved in protein synthesis and degradation (Cao et al., 2018). On the other hand, in the polychaete *P. dumerilii* genes encoding proteins related to the synthesis of proteins and DNA replication were up-regulated after 7 d of exposition to pH 7.8 (Wäge et al., 2016). Moreover, in specimens of *P. lividus* inhabiting naturally acidified sites (pH 7.8) genes encoding proteins involved in amino-acid degradation were up-regulated (Migliaccio et al., 2019).

As part of the central nervous system, the cholinergic signaling is involved in numerous brain functions (Das et al., 2005) as well as in development (Abreu-Villaça et al., 2011). Alterations in the cholinergic complex are associated with changes in behavior and diseases in organisms (SawKatare et al., 2020; Bianchini et al., 2022). In the Yesso scallop *Patinopecten yessoensis* the cholinergic pathway was differently regulated in response to pH 7.5, 6.5 over time (0, 3, 6, 12 and 24 h). All the ten *P. yessoensis'* cholinesterase genes (*PyChEs*) targeted resulted differentially expressed in specimens exposed to low pH compared to controls and most of them were found initially up-regulated suggesting the involvement in an acute response towards low-pH conditions (Xing et al., 2021).

Apoptosis represents another crucial pathway to maintain internal homeostasis and its excessive or insufficient regulation may have serious consequences on organisms, such as occurrence of tumors or autoimmune diseases as described in humans (Alberts et al., 2008). An up-regulation of proteins involved in programmed cell death, apoptosis, was reported at low pH exposure in *C. gigas* after 31 d to pH 7.6 (Cao et al., 2018).

All former evidences suggest that low pH conditions affect several cellular responses with compensatory mechanisms and detrimental effects based on time of exposure (short- *vs* long-term), range of pH and sensitivity of the selected species and cell investigated. At the cellular level there are also other mechanisms conferring tolerance/resistance towards changes in the external environment and particularly relevant are those at membrane level. It stands out the adenosine triphosphate (ATP)-binding cassette (ABC) transporters involved in drug and/or xenobiotic resistance, already well known in numerous taxa including marine species. Their role towards acid stress tolerance has recently attracted the attention of the scientific community since they can confer resistance to acid stress conditions which are those natural marine species are facing in present and future OA scenarios. Here we aim to review the current knowledge on ABC transport proteins and recent stimulating findings on their involvement in acid stress resistance in some organisms.

3. ATP-binding cassette (ABC) transporters and their involvement in acid stress resistance

ABC transporters are a large protein superfamily highly conserved across taxa (Li and Nikaido, 2004; Annilo et al., 2006; Rea, 2007; Jeong et al., 2017). ABC efflux proteins act in many cases as transmembrane pumps which use the energy from ATP hydrolysis for their activity. They control the trafficking of chemicals across membranes and regulate cellular processes, such as DNA repair (Goosen and Moolenaar, 2001) and translational regulation (Chakraburtty, 2001). ABC transporters fulfill cellular functions in nutrient uptake, protein synthesis regulation and translocation, and cytoplasmic pH control (Chen et al., 2006; Igarashi and Kashiwagi, 1999; Sangari et al., 2010; Schinkel et al., 1994). By transferring substances, they contribute to maintain cellular equilibrium conditions. ABC transporters are located in plasma and intracellular membranes and can be organized as full transporters with two nucleotide-binding (with Walker A and B domains and a peculiar signature motif) and transmembrane domains (with α-helix transmembrane segments), or as half transporters, containing one nucleotide-binding and one transmembrane domain (Hyde et al., 1990). A variety of chemicals can act as substrates, such as nutrients, xenobiotics and other exogenic compounds, endogenous compounds and metabolites of endogenous and exogenous compounds including metabolized drugs and xenobiotics (Deeley et al., 2006; Gottesman and Pastan, 1993; Igarashi and Kashiwagi, 1999). The transfer across extra- and intracellular membranes influences substrate bioavailability (Ayrton and Morgan, 2001; Dietrich et al., 2003).

ABC transporter subfamilies ABCA – ABCG were found in all animal taxa; subfamily ABCH was so far found only in one vertebrate species, the zebrafish (*Danio rerio*) (Dean and Annilo, 2005; Popovic et al., 2010); subfamily ABCJ was recently proposed as separate group including nine proteins in the mosquito *Aedes aegypti* (Figueira-Mansur et al., 2020). ABCA subfamily paralogs are mainly involved in the transfer of lipids across cellular membranes (Dassa and Bouige, 2001) while ABCB

Table 3
List of marine species where P-glycoprotein-like and multidrug-associated proteins have been identified. The life stage, tissues and organs of studied organisms where the ABC proteins have been studied is also reported.

Species	Life stage/tissue/organ	Gene subfamily	References
Tethya aurantium	–	P-gp	Kurelec, 1992
Verongia aerophoba	–	P-gp	Kurelec, 1992
Geodia cydonium	–	P-gp	Kurelec, 1992
Mytilus edulis	Embryos and larvae	MDR	McFadzen et al., 2000
Mytilus californianus	Gills	ABCB, ABCC	Luckenbach and Epel, 2008
Mytilus galloprovincialis	Gills, Mantle, Digestive gland	P-gp	Kurelec, 1992
Urechis caupo	Embryos and larvae	MXR	Hamdoun et al., 2002
Asterina miniata	Oocytes	P-gp-like, MRP	Roepke et al., 2006
Pisaster ochraceous	Oocytes	P-gp-like, MRP	Roepke et al., 2006
Strongylocentrotus purpuratus	Embryos	ABCB1, ABCC1	Hamdoun et al., 2004
Echinometra lucunter	Gametes and embryos	ABCB1, ABCC1	De Souza et al., 2010
Ciona intestinalis	–	ABCB1, ABCB11, ABCC1, ABCC2, ABCC4, ABCC10, ABCC12, ABCG2	Annilo et al., 2006
Petromyzon marinus	Rope, Lips, Supraneural tissue, Neutrophils, Monocytes, Gil, Eye, Skin, Muscle, Intestine, Kidney, Liver	ABCB1, ABCB11, ABCC1, ABCC2, ABCC3, ABCC4, ABCC5, ABCC7, ABCC8, ABCC9, ABCC10, ABCG2	Ren et al., 2015
Chelon labrosus	Liver, Brain	ABCB1, ABCB11, ABCC2, ABCC3, ABCG2	Díaz de Cerio et al., 2012
Dicenthrarchus labrax	Liver	ABCB1, ABCC1, ABCC2, ABCG2	Ferreira et al., 2014
Mullus barbatus	Liver	MRP	Sauerborn et al., 2004
Oncorhynchus mykiss	Liver, Brain, Gonads, Kidney, Gills, Proximal Intestine, Distal Intestine	ABCB1, ABCB11, ABCC1, ABCC2, ABCC3, ABCC4, ABCC5, ABCG2	Lončar et al., 2010
Plactichthys flesus	Liver, Gills and Proximal intestine	ABCB1b, ABCB11, ABCC1, ABCC2, ABCG2	Costa et al., 2012
Pleuronectes americanus	–	P-gp	Chan et al., 1992
Scophtalmus maximus	Gills, Brain, Heart, Liver, Intestine, Muscle, Esophagus, Kidney	P-gp, MDR	Tutundjian et al., 2002
Trematomus bernacchii	Liver	ABCB1, ABCC1, ABCC2, ABCC4, ABCC9	Zucchi et al., 2010

Abbreviations in the table: P-glycoprotein (P-gp); multidrug resistance (MDR); multixenobiotic resistance (MXR); multidrug resistance-associated protein (MRP).

subfamily, as for instance the ABCB1 transporter, known as P-glycoprotein, plays an important role in multidrug and multixenobiotic resistance (MDR and MXR, respectively) by regulating also the entrance of drugs and xenobiotics, thus identified as phase 0 of cellular biotransformation (Homolya et al., 1993). They have low specificity to substrates because of a wide binding cavity and a great flexibility (Aller et al., 2009) and can translocate various compounds with moderate hydrophobicity, low molecular weight and positive or neutral residues (Higgins, 2007; Litman et al., 2001; McDevitt and Callaghan, 2007). This is considered an adaptive mechanism, which also confers higher resistance to multiple chemical stressors and it is recognized as the first line of cellular defense (Epel et al., 2008). Members of the large ABCC subfamily generally transport metabolites, eliminating modified endogenous and exogenous compounds from cells (Cole and Deeley, 1998; Deeley et al., 2006; Haimeur et al., 2004). Functions of the subfamily ABCD paralogs are largely unclear; some of them were found to be involved in the uptake of peroxisome fatty acid and are supposed to have important physiological roles (Annilo et al., 2006; Baker et al., 2015). Members of the subfamilies ABCE and ABCF participate in the regulation of protein synthesis (Chen et al., 2006), ABCF paralogs are furthermore involved in ribosome assembly and protein transduction (Annilo et al., 2006). The ABCG and ABCH subfamilies show high structural similarity but the functions of the ABCH subfamily are little known (Dean and Annilo, 2005; Popovic et al., 2010).

ABC transporters from the ABCB, ABCC and ABCG subfamilies (ABCB1, ABCC1, ABCC2, ABCG2) were found to be involved in MDR of cancer cells (Gros et al., 1986; Juliano and Ling, 1976; Roninson et al., 1984) and healthy tissues (Leslie et al., 2005); orthologs of these transporters were observed to confer MXR, a term primarily used for the resistance of aquatic taxa against toxicants in their environment (Bard, 2000; Kurelec, 1992; Epel, 1998; Hamdoun et al., 2004; Luckenbach and Epel, 2008; Sun et al., 2017). By providing a cellular stress response as part of the MDR and MXR systems, they limit the intracellular accumulation of toxic compounds (Annilo et al., 2006; Corsi and Marques-Santos, 2018). Such involvement of ABC transporters in MXR processes in aquatic species resulted in a prominent ecotoxicological relevance (Corsi and Marques-Santos, 2018; Epel et al., 2008). Overviews on marine taxa and life stages, in which ABC transporters have been investigated in MXR functioning, but also in other contexts, are given in Table 3 and Fig. 3.

MDR/MXR related ABC transporters generally recognize a wide range of chemically diverse compounds as substrates that they translocate across cellular membranes (Higgins, 2007; Litman et al., 2001; McDevitt and Callaghan, 2007; Aller et al., 2009; Leslie et al., 2005). Other paralogs from these subfamilies show more substrate specificity, limiting transmembrane translocation to certain physiologically relevant compounds, such as for instance the bile acid transporter ABCB11 (Gerloff et al., 1998; Cai et al., 2001).

Cellular stress responses carried out by the ABC proteins result from an up regulation of the protective and detoxifying corresponding genes (Epel et al., 2008). Therefore, the MXR constitutes a mechanism of adaptation for aquatic organisms that enables them to live and growth in a polluted environment. A relationship between exposure to xenobiotics and marine toxins and the ABC genes expression level was documented (Huang et al., 2015; Tanaka et al., 2002). MDR genes are also induced by other stress signals, as heat shock, inflammation, hypoxia, UV and X irradiation and exposure to carcinogens (Epel et al., 2008).

In mollusks, gill ABCB- and ABCC-types transporters manage the trafficking of nutrients and prevent the entrance of toxic compounds in the body, so they represent an important external barrier between the environment and the organism and have a crucial role in the maintenance of homeostasis in sensitive tissues (Luckenbach and Epel, 2008). In addition, a comparative genetic study between shallow and abyssal mussel genome showed that these proteins have a role in adaptation to the deep-sea environment (Sun et al., 2017). Roepke et al. (2006) described that ABC proteins contribute to oocyte maturation in the sea

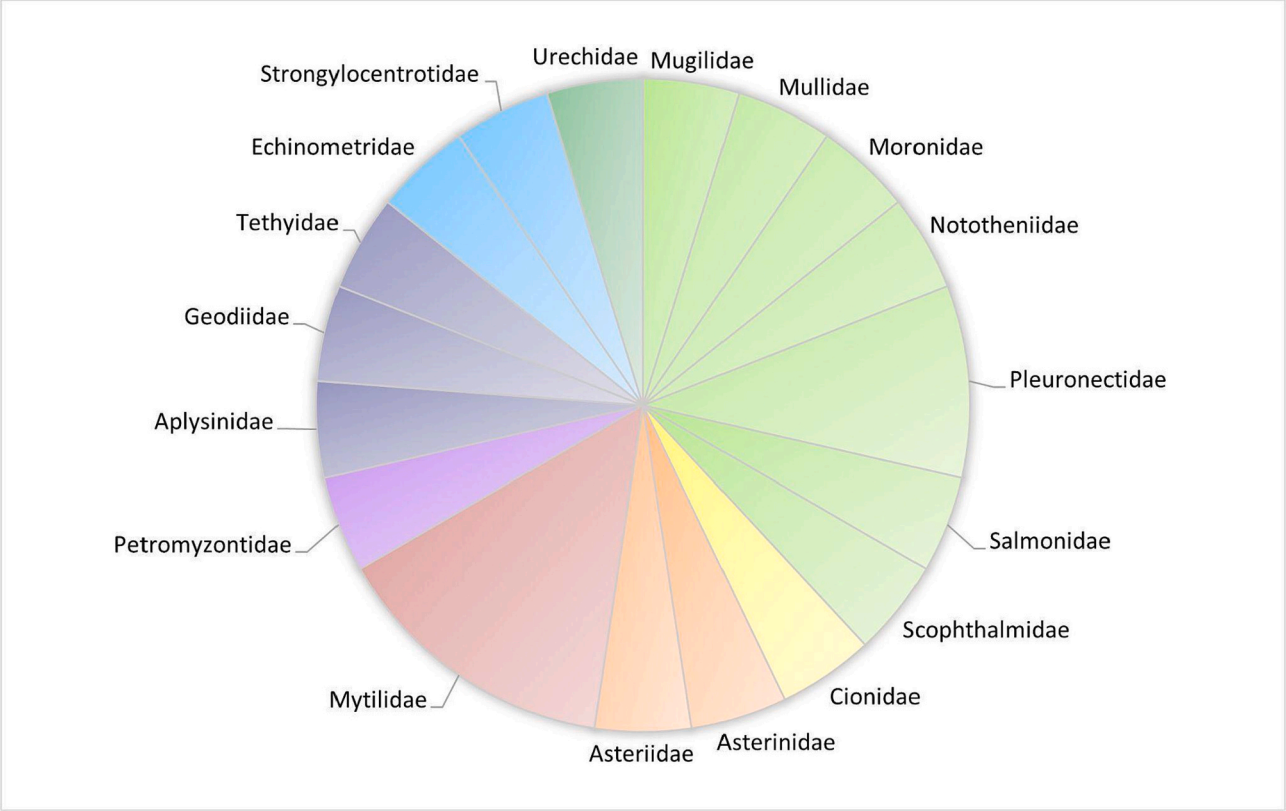

Fig. 3. Families of marine species where P-glycoproteins/NDR-like genes have been identified. Colors refer to: Actinopterygii (light green), Ascidiacea (yellow), Asteroidea (orange), Bivalvia (red), Cephalaspidomorphi (purple), Demospongiae (dark blue), Echinoidea (light blue) and Polychaeta (dark green). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

stars *Patiria miniata* (formerly known as *Asterina miniata*) and *Pisaster ochraceous*. The ABC pumps in sea urchin gametes, embryos and pluteus play an important biochemical role in early life stage development. They constitute a defense barrier against toxicants and contribute to the homeostasis of cell membranes. Also, they carry endogenous signaling molecules essential for embryonic development and may be involved in gametes fusion (Corsi and Marques-Santos, 2018).

In bacterial cells the ABC transporters showed to play a role in the tolerance to acid stress conditions. Survival of bacteria - such as the Cyanobacteria *Synechocystis* sp. (Matsuhashi et al., 2015; Tahara et al., 2012, 2015; Uchiyama et al., 2019) and *Anabaena* sp. (Shvarev and Maldener, 2020) or the Firmicutes *Lactococcus lactis* (Zhu et al., 2019) - in acidified environments could be granted by the presence of these pumps. Some researchers have suggested that the tolerance to acid stress in bacteria is due to the transport of substances, like ATP and carbohydrates, by the ABC proteins (Zhu et al., 2019). The cyanobacterium *Synechocystis* sp. PCC 6803 was selected for its remarkable acid stress tolerance and results revealed that several ABC genes might be involved. In this species, Tahara et al. (2012, 2015) found that ABC transporter subunits *Slr1045*, *Sll0751* and *Sll1041* were essential for survival in acidic environments (tested at pH 6.0 units). Particularly, they observed that these three proteins form a lipid transport complex that is involved in stress tolerance. Matsuhashi et al. (2015) also recognized *Slr2019* as an important ABC protein for acid stress tolerance (pH 6.0). This is a homolog to *MsbA* in *Escherichia coli* which is an inner membrane transporter involved in the export of phospholipids and lipid A, the endotoxic component of the lipopolysaccharides. Even though expression of *Slr2019* gene was not affected and the amount of Slr2019 protein was not increased under acid stress, this protein was found to be important for the survival and growth in acidified conditions. The extracellular lipid transport could represent a mechanism carried out by bacteria forming a layer able to protect cells. A similar process occurs in bile ducts of mammals where phosphatidylcholine (PC) was flopped out from the hepatocytes by a P- glycoprotein, the ABCB4 transporters. Once in the biliary tree, PCs form a mixed micelle with the bile acids to neutralize its toxicity towards hepatocytes (Barrios and Lichtenberger, 2000; Borst et al., 2000; Linton, 2015; Nicolaou et al., 2012).

Still within *Synechocystis* sp. PCC 6803, Uchiyama et al. (2019) suggested another ABC protein complex engaged in acid stress tolerance (at pH 6.0), composed by three proteins: *Sll1180*, facilitating growth of bacterial cells in acid conditions and which is upregulated after acid treatment, *Sll1181*, homologous to *HlyD* of *Escherichia coli*, and *Slt1270*, that has homology with *TolC* of *E. coli* and transports the negatively charged *Sll1951* out of the cell. Once outside the cell, *Sll1951* might attract H^+ and constitute an essential factor in acid stress tolerance. Recently, the mechanisms of resistance to low pH have also been studied in the filamentous cyanobacterium *Anabaena* sp. PCC 7120 analyzing the role of gene *all5304* in acid stress tolerance (Shvarev and Maldener, 2020). Protein *All5304* shows homology with 100 % probability to *Sll1181* from *Synechocystis* sp., which is an ABC transporter involved in acid stress resistance (Uchiyama et al., 2019), as previously mentioned. Through an experiment of DNA manipulation, in which *all5304* gene has been silenced, Shvarev and Maldener (2020) have described the inability for the mutant strain to survive in a low-pH environment (pH 6.0). These results evidenced that the *all5304* gene plays a role in acid tolerance by regulating a possible component of a complex exporting an effector protein that takes part in the formation of extracellular structures involved in resistance to low pH. Another species examined for its acid stress tolerance (pH 4.0) is *Lactococcus lactis*. Zhu et al. (2019) indicated overexpression of genes encoding for MsmK, a sugar ABC transporter ATP-binding protein, DppA, an oligopeptide ABC transporter substrate-binding protein, and RbsA and RbsB, that compose

(with RbsCD protein) a D-ribose ABC transporter substrate-binding proteins, demonstrating the involvement of ABC pumps in *L. lactis* acid stress tolerance.

To the best of our knowledge, just one study has investigated changes in genes encoding ABC transporters in oysters after exposure to acid stress (Wang et al., 2020). Wang et al. (2020) have identified the up-regulation of ABC transporter genes in hemocytes of the Pacific oyster *C. gigas* chronically exposed to high-CO_2 levels. Analysis of the gene ontology (GO) distribution of differentially expressed genes has shown that ABC genes affected by long-term exposure to low pH belong to two different GO categories. In particular, ABC transporter G family member 14 and multidrug resistance protein 1 belong to the membrane and to the heterocyclic compound binding category (GO:0016020 and GO:1901363), and ABC subfamily A member 1 and 3 belong to the heterocyclic compound binding category (GO:1901363).

These examples show that the knowledge of mechanisms of acid stress tolerance may contribute to understand if and how marine species can cope with OA, which would be crucial to define future scenarios on the impact of OA on aquatic life.

4. Final remarks

Studies on natural acidified environments show that low pH conditions influence different hierarchical scales of biological complexity, from the cellular and species level to populations, communities and ecosystems. The cellular processes most directly affected by decreased seawater pH are related to calcification, metabolism, immune function and antioxidant responses that may impair physiological functions, growth, reproduction and survival. Decreased seawater pH can result in weakening of the whole organism by affecting an organism's internal homeostasis in a species-dependent manner. Indirectly, decreased seawater pH can also affects marine plants and animals' intra-specific communication, feeding habits, defenses against predators (with impacts on predator-prey relationships), deeply modifying the structure of animal and plant communities. Certain marine species appear to be able to cope with lowered pH conditions due to the action of a cellular defense mechanism based on ABC transporters. Acid stress tolerance conferred by these proteins may be related to the transport of certain substances, including ATP, carbohydrates, lipids and proteins. Further information will be essential to understand the cellular mechanisms taking part in resistance and adaptation to acidified environments in order to unravel consequences of OA.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.marpolbul.2022.114365.

Funding

This work was supported by the 2020 scholarship co-founded by the University of Siena and the Stazione Zoologica Anton Dohrn of Naples entitled 'Molecular bases and evolutionary constraints of cellular acid tolerance in cyanobacteria and invertebrates subjected to ocean acidification and other sources of stress' in the framework of the Doctoral Research Program in Environmental, Geological and Polar Sciences and Technologies (36th cycle) of the University of Siena.

Declaration of competing interest

The authors declare no competing interests.

Data availability

Data will be made available on request.

References

Abreu-Villaça, Y., Filgueiras, C.C., Manhães, A.C., 2011. Developmental aspects of the cholinergic system. Behav. Brain Res. 221, 367–378. https://doi.org/10.1016/j.bbr.2009.12.049.

Adey, W.H., Loveland, K., 2007. Biomineralization and calcification: a key to biosphere and ecosystem function. In: Adey, W.H., Loveland, K. (Eds.), Dynamic Aquaria. Building and Restoring Living Ecosystems. Academic Press. https://doi.org/10.1016/B978-0-12-370641-6.X5000-6.

Agostini, A., Harvey, B.P., Wada, S., Kon, K., Milazzo, M., Inaba, K., Hall-Spencer, J.M., 2018. Ocean acidification drives community shifts towards simplified non-calcified habitats in a subtropical-temperate transition zone. Sci. Rep. 8, 11354. https://doi.org/10.1038/s41598-018-29251-7.

Alber, A.B., Suter, D.M., 2019. Dynamics of protein synthesis and degradation through the cell cycle. Cell Cycle 18 (8), 784–794. https://doi.org/10.1080/15384101.2019.1598725.

Alberts, B., Johnson, A., Lewis, J., Raff, M., Roberts, K., Walter, P., 2008. Molecular Biology of the Cell, 5th ed. Garland Science.

Albright, R., Mason, B., Miller, M., Langdon, C., 2010. Ocean acidification compromises recruitment success of the threatened Caribbean coral *Acropora palmata*. Proc. Natl. Acad. Sci. U. S. A. 107 (47), 20400–20404. https://doi.org/10.1073/pnas.1007273107.

Albright, R., Takeshita, Y., Koweek, D.A., Ninokawa, A., Wolfe, K., Rivlin, T., Nebuchina, Y., Young, J., Caldeira, K., 2018. Carbon dioxide addition to coral reef waters suppresses net community calcification. Nature 555, 516–519. https://doi.org/10.1038/nature25968.

Aller, S.G., Yu, J., Ward, A., Weng, Y., Chittaboina, S., Zhuo, R., Harrell, P.M., Trinh, Y. T., Zhang, Q., Urbatsch, I.L., Chang, G., 2009. Structure of P-glycoprotein reveals a molecular basis for poly-specific drug binding. Science 323 (5922), 1718–1722. https://doi.org/10.1126/science.1168750.

Annilo, T., Chen, Z.-Q., Shulenin, S., Costantino, J., Thomas, L., Lou, H., Stefanov, S., Dean, M., 2006. Evolution of the vertebrate ABC gene family: analysis of gene birth and death. Genomics 88, 1–11. https://doi.org/10.1016/j.ygeno.2006.03.001.

Ayrton, A., Morgan, P., 2001. Role of transport proteins in drug absorption, distribution and excretion. Xenobiotica 31 (8/9), 469–497. https://doi.org/10.1080/00498250110060969.

Baker, A., Carrier, D.J., Schaedler, T., Waterham, H.R., van Roermund, C.W., Theodoulou, F.L., 2015. Peroxisomal ABC transporters: functions and mechanism. Biochem. Soc. Trans. 43, 959–965. https://doi.org/10.1042/BST20150127.

Bard, S.M., 2000. Multixenobiotic resistance as a cellular defense mechanism in aquatic organisms. Aquat. Toxicol. 48 (4), 357–389. https://doi.org/10.1016/s0166-445x(00)00088-6.

Barrios, J.M., Lichtenberger, L.M., 2000. Role of biliary phosphatidylcholine in bile acid protection and NSAID injury of the ileal mucosa in rats. Gastroenterology 118, 1179–1186. https://doi.org/10.1053/gast.2000.7953.

Barruffo, A., Ciaralli, L., Ardizzone, G., Gambi, M.C., Casoli, E., 2021. Ocean acidification and molluscs settlement in *Posidonia oceanica* meadows: does the seagrass buffer low pH effects at CO_2 vents? Diversity 13, 311. https://doi.org/10.3390/d13070311.

Bates, N.R., Astor, Y.M., Church, M.J., Currie, K., Dore, J.E., González-Dávila, M., Lorenzoni, L., Muller-Karger, F., Olafsson, J., Santana-Casiano, J.M., 2014. A time-series view of changing ocean chemistry due to ocean uptake of anthropogenic CO_2 and ocean acidification. Oceanography 27 (1), 126–141. https://doi.org/10.5670/oceanog.2014.16.

Bianchini, M.C., Soares, L.S.W., Sousa, J.M.F.M., Ramborger, B.P., Gayer, M.C., Bridi, J. C., Roehrs, R., Pinton, S., Aschner, M., Avila, D.S., Puntel, R.L., 2022. MeHg exposure impairs both the catecholaminergic and cholinergic systems resulting in motor and non-motor behavioral changes in *Drosophila melanogaster*. Chem. Biol. Interact. 365, 110121 https://doi.org/10.1016/j.cbi.2022.110121.

Bindoff, N.L., Cheung, W.W.L., Kairo, J.G., Arístegui, J., Guinder, V.A., Hallberg, R., Hilmi, N., Jiao, N., Karim, M.S., Levin, L., O'Donoghue, S., Purca Cuicapusa, S.R., Rinkevich, B., Suga, T., Tagliabue, A., Williamson, P., 2019. Changing ocean, marine ecosystems, and dependent communities. In: Pörtner, H.-O., Roberts, D.C., Masson-Delmotte, V., Zhai, P., Tignor, M., Poloczanska, E., Mintenbeck, K., Alegría, A., Nicolai, M., Okem, A., Petzold, J., Rama, B., Weyer, N.M. (Eds.), IPCC Special Report on the Ocean and Cryosphere in a Changing Climate. In press.

Borst, P., Zelcer, N., van Helvoort, A., 2000. ABC transporters in lipid transport. Biochim. Biophys. Acta Mol. Cell Biol. Lipids 1486 (1), 128–144. https://doi.org/10.1016/s1388-1981(00)00053-6. Doi:

Brewer, P.G., 1997. Ocean chemistry of the fossil fuel CO_2 signal: the haline signal of "business as usual". Geophys. Res. Lett. 24 (11), 1367–1369. https://doi.org/10.1029/97GL01179.

Burns, W.C.G., 2008. Anthropogenic carbon dioxide emissions and ocean acidification: the potential impacts on ocean biodiversity. In: Askins, R.A., Dreyer, G.D., Visgilio, G.R., Whitelaw, D.M. (Eds.), Saving Biological Diversity. Springer, Boston, MA. https://doi.org/10.1007/978-0-387-09565-3_14.

Burton, G.J., Jauniaux, E., 2011. Oxidative stress. Best Pract. Res. Clin. Obstet. Gynaecol. 25 (3), 287–299. https://doi.org/10.1016/j.bpobgyn.2010.10.016.

Cai, S.Y., Wang, L., Ballatori, N., Boyer, J.L., 2001. Bile salt export pump is highly conserved during vertebrate evolution and its expression is inhibited by PFIC type II mutations. Am. J. Physiol. Gastrointest. Liver Physiol. 281, G316–G322. https://doi.org/10.1152/ajpgi.2001.281.2.G316.

Caldeira, K., Wickett, M.E., 2003. Anthropogenic carbon and ocean pH. Nature 425, 365. https://doi.org/10.1038/425365a.

Calosi, P., Rastrick, S.P.S., Lombardi, C., de Guzman, H.J., Davidson, L., Jahnke, M., Giangrande, A., Hardege, J.D., Schulze, A., Spicer, J.I., Gambi, M.-C., 2013. Adaptation and acclimatization to ocean acidification in marine ectotherms: an in

situ transplant experiment with polychaetes at a shallow CO_2 vent system. Philos. Trans. R. Soc. B 368, 20120444. https://doi.org/10.1098/rstb.2012.0444.
Cao, L., Caldeira, K., Jain, A.K., 2007. Effects of carbon dioxide and climate change on ocean acidification and carbonate mineral saturation. Geophys. Res. Lett. 34, L05607 https://doi.org/10.1029/2006GL028605.
Cao, R., Wang, Q., Yang, D., Liu, Y., Ran, W., Qua, Y., Wu, H., Cong, M., Li, F., Ji, C., Zhao, J., 2018. CO2-induced ocean acidification impairs the immune function of the Pacific oyster against *Vibrio splendidus* challenge: an integrated study from a cellular and proteomic perspective. Sci. Total Environ. 625, 1574–1583. https://doi.org/10.1016/j.scitotenv.2018.01.056.
Chakraburtty, K., 2001. Translational regulation by ABC systems. Res. Microbiol. 152, 391–399. https://doi.org/10.1016/s0923-2508(01)01210-4.
Chan, K.M., Davies, P.L., Childs, S., Veinot, L., Ling, V., 1992. P-glycoprotein genes in the winter flounder, *Pleuronectes americanus*: isolation of two types of genomic clones carrying 3' terminal exons. Biochim. Biophys. Acta 1171, 65–72. https://doi.org/10.1016/0167-4781(92)90140-u.
Chen, Z., Dong, J., Ishimura, A., Daar, I., Hinnebusch, A.G., Dean, M., 2006. The essential vertebrate ABCE1 protein interacts with eukaryotic initiation factors. J. Biol. Chem. 281 (11), 7452–7457. https://doi.org/10.1074/jbc.M510603200.
Chierici, M., Fransson, A., 2009. Calcium carbonate saturation in the surface water of the Arctic Ocean: undersaturation in freshwater influenced shelves. Biogeosciences 6, 2421–2432. https://doi.org/10.5194/bg-6-2421-2009.
Cigliano, M., Gambi, M.C., Rodolfo-Metalpa, R., Patti, F.P., Hall-Spencer, J.M., 2010. Effects of ocean acidification on invertebrate settlement at volcanic CO_2 vents. Mar. Biol. 157, 2489–2502. https://doi.org/10.1007/s00227-010-1513-6.
Cole, S.P.C., Deeley, R.G., 1998. Multidrug resistance mediated by the ATP-binding cassette transporter protein MRP. BioEssays 20 (11), 931–940. https://doi.org/10.1002/(SICI)1521-1878(199811)20:11<931::AID-BIES8>3.0.CO;2-J.
Corsi, I., Marques-Santos, L.F., 2018. Ecotoxicology in marine environments: the protective role of ABC transporters in sea urchin embryos and larvae. In: Carrier, T. J., Reitzel, A.M., Heyland, A. (Eds.), Evolutionary Ecology of Marine Invertebrate Larvae. Oxford University Press. https://doi.org/10.1093/oso/9780198786962.003.0018.
Costa, J., Reis-Henriques, M.A., Castro, L.F.C., Ferreira, M., 2012. Gene expression analysis of ABC efflux transporters, CYP1A and GSTα in Nile tilapia after exposure to benzo(a)pyrene. Comp. Biochem. Physiol. C 155, 469–482. https://doi.org/10.1016/j.cbpc.2011.12.004.
Crook, E.D., Kroeker, K.J., Potts, D.C., Rebolledo-Vieyra, M., Hernandez-Terrones, L.M., Paytan, A., 2016. Recruitment and succession in a tropical benthic community in response to in-situ ocean acidification. PLoS ONE 11 (1), e0146707. https://doi.org/10.1371/journal.pone.0146707.
D'Amario, B., Pérez, C., Grelaud, M., Pitta, P., Krasakopoulou, E., Ziveri, P., 2020. Coccolithophore community response to ocean acidification and warming in the eastern Mediterranean Sea: results from a mesocosm experiment. Sci. Rep. 10 (1), 12637. https://doi.org/10.1038/s41598-020-69519-5.
Das, A., Dikshit, M., Nath, C., 2005. Role of molecular isoforms of acetylcholinesterase in learning and memory functions. Pharmacol. Biochem. Behav. 81, 89–99. https://doi.org/10.1016/j.pbb.2005.02.006.
Dassa, E., Bouige, P., 2001. The ABC of ABCs: a phylogenetic and functional classification of ABC systems in living organisms. Res. Microbiol. 152, 211–229. https://doi.org/10.1016/S0923-2508(01)01194-9.
De Souza, M.Q.V., Barros, T.V., Torrezan, E., Cavalcanti, A.L., Figueiredo, R.C., Marques-Santos, L.F., 2010. Characterization of functional activity of ABCB1 and ABCC1 proteins in eggs and embryonic cells of the sea urchin *Echinometra lucunter*. Biosci. Rep. 30 (4), 257–265. https://doi.org/10.1042/BSR20090081.
Dean, M., Annilo, T., 2005. Evolution of the ATP-binding cassette (ABC) transporter superfamily in vertebrates. Annu. Rev. Genomics Hum. Genet. 6, 123–142. https://doi.org/10.1146/annurev.genom.6.080604.162122.
Deeley, R.G., Westlake, C., Cole, S.P.C., 2006. Transmembrane transport of endo- and xenobiotics by mammalian ATP-binding cassette multidrug resistance proteins. Physiol. Rev. 86, 849–899. https://doi.org/10.1152/physrev.00035.2005.
DeVries, T., Le Quéré, C., Andrews, O., Berthet, S., Hauck, J., Ilyina, T., Landschützer, P., Lenton, A., Lima, I.D., Nowicki, M., Schwinger, J., Séférian, R., 2019. Decadal trends in the ocean carbon sink. Proc. Natl. Acad. Sci. 116 (24), 11646–11651. https://doi.org/10.1073/pnas.1900371116.
Di Giglio, S., Agüera, A., M'Zoudi, S., Angulo-Preckler, C., Avila, C., Dubois, P.H., Pernet, P.H., 2021. Effects of ocean acidification on acid-base physiology, skeleton properties, and metal contamination in two echinoderms from vent sites in Deception Island, Antarctica. Sci. Total Environ. 765, 142669 https://doi.org/10.1016/j.scitotenv.2020.142669.
Diaz de Cerio, O., Bilbao, E., Cajaraville, M.P., Cancio, I., 2012. Regulation of xenobiotic transporter genes in liver and brain of juvenile thicklip grey mullets (*Chelon labrosus*) after exposure to prestige-like fuel oil and to perfluorooctane sulfonate. Gene 498, 50–58. https://doi.org/10.1016/j.gene.2012.01.067.
Dietrich, C.G., Geier, A., Oude Elferink, R.P.J., 2003. ABC of oral bioavailability: transporters as gatekeepers in the gut. Gut 52 (12), 1788–1795. https://doi.org/10.1136/gut.52.12.1788.
Dineshram, R., Quan, Q., Sharma, R., Chandramouli, K., Yalamanchili, H.K., Chu, I., Thiyagarajan, V., 2015. Comparative and quantitative proteomics reveal the adaptive strategies of oyster larvae to ocean acidification. Proteomics 15, 4120–4134. https://doi.org/10.1002/pmic.201500198.
Dineshram, R., Thiyagarajan, V., Lane, A., Ziniu, Y., Xiao, S., Leung, P.T.Y., 2013. Elevated CO_2 alters larval proteome and its phosphorylation status in the commercial oyster, *Crassostrea hongkongensis*. Mar. Biol. 160, 2189–2205. https://doi.org/10.1007/s00227-013-2176-x.
Doney, S.C., Fabry, Fabry V.J., Feely, R.A., Kleypas, J.A., 2009. Ocean acidification: the other CO_2 problem. Annu. Rev. Mar. Sci. 1, 169–192. https://doi.org/10.1146/annurev.marine.010908.16383.
Dupont, S., Dorey, N., Thorndyke, M., 2010. What meta-analysis can tell us about vulnerability of marine biodiversity to ocean acidification? Estuar. Coast. Shelf Sci. 89, 182–185. https://doi.org/10.1016/j.ecss.2010.06.013.
Duquette, A., McClintock, J.B., Amsler, C.D., Pérez-Huerta, A., Milazzo, M., Hall-Spencer, J.M., 2017. Effects of ocean acidification on the shells of four Mediterranean gastropod species near a CO_2 seep. Mar. Pollut. Bull. 124 (2), 917–928. https://doi.org/10.1016/j.marpolbul.2017.08.007.
Epel, D., 1998. Use of multidrug transporters as first lines of defense against toxins in aquatic organisms. Comp. Biochem. Physiol. A Mol. Integr. Physiol. 120 (1), 23–28. https://doi.org/10.1016/S1095-6433(98)10005-3.
Epel, D., Luckenbach, T., Stevenson, C.N., Macmanus-Spencer, L.A., Hamdoun, A.M., Smital, T., 2008. Efflux transporters: newly appreciated roles in protection against pollutants. Environ. Sci. Technol. 42 (11), 3914–3920. https://doi.org/10.1021/es087187v.
Fabricius, K.E., Langdon, C., Uthicke, S., Humphrey, C., Noonan, S., De'ath, G., Okazaki, R., Muehllehner, N., Glas, M.S., Lough, J.M., 2011. Losers and winners in coral reefs acclimatized to elevated carbon dioxide concentrations. Nat. Clim. Chang. 1, 165–169. https://doi.org/10.1038/nclimate1122.
Esposito, V., Auriemma, R., De Vittor, C., Relitti, F., Urbini, L., Kralj, M., Gambi, M.C., 2022. Structural and functional analyses of motile fauna associated with *Cystoseira brachycarpa* along a gradient of ocean acidification in a CO_2-vent system off panarea (Aeolian Islands, Italy). J. Mar. Sci. Eng. 10, 451. https://doi.org/10.3390/jmse10040451.
Fabricius, K.E., De'ath, G., Noonan, S., Uthicke, S., 2014. Ecological effects of ocean acidification and habitat complexity on reef-associated macroinvertebrate communities. Proc. R. Soc. B 281, 20132479. https://doi.org/10.1098/rspb.2013.2479.
Falini, G., Fermania, S., Goffredo, S., 2015. Coral biomineralization: a focus on intra-skeletal organic matrix and calcification. Semin. Cell Dev. Biol. 46, 17–26. https://doi.org/10.1016/j.semcdb.2015.09.005.
Ferreira, M., Santos, P., Rey-Salgueiro, L., Zaja, R., Reis-Henriques, M.A., Smital, T., 2014. The first demonstration of CYP1A and the ABC protein(s) gene expression and activity in european seabass (*Dicentrarchus labrax*) primary hepatocytes. Chemosphere 100, 152–159. https://doi.org/10.1016/j.chemosphere.2013.11.051.
Figueira-Mansur, J., Schrago, C.G., Salles, T.S., Alvarenga, E.S.L., Vasconcellos, B.M., Melo, A.C.A., Moreira, M.F., 2020. Phylogenetic analysis of the ATP-binding cassette proteins suggests a new ABC protein subfamily J in *Aedes aegypti* (Diptera: Culicidae). BMC Genomics 21, 463. https://doi.org/10.1186/s12864-020-06873-8.
Foo, S.A., Byrne, M., Ricevuto, E., Gambi, M.C., 2018. The carbon dioxide vents of Ischia, Italy, a natural system to assess impacts of ocean acidification on marine ecosystems: an overview of research and comparisons with other vent systems. Oceanogr. Mar. Biol. Annu. Rev. 56, 237–310.
Freitas, R., Pires, A., Moreira, A., Wrona, F.J., Figueira, E., Soares, A.M.V.M., 2016a. Biochemical alterations induced in *Hediste diversicolor* under seawater acidification conditions. Mar. Environ. Res. 117, 75–84. https://doi.org/10.1016/j.marenvres.2016.04.003.
Freitas, R., Pires, A., Veleza, C., Almeida, A., Moreira, A., Wrona, F.J., Soares, A.M.V.M., Figueira, E., 2016b. Effects of seawater acidification on *Diopatra neapolitana* (Polychaete, Onuphidae): biochemical and regenerative capacity responses. Ecol. Indic. 60, 152–161. https://doi.org/10.1016/j.ecolind.2015.06.032.
Gambi, M.C., Musco, L., Giangrande, A., Badalamenti, F., Micheli, F., Kroeker, K.J., 2016. Distribution and functional traits of polychaetes in a CO_2 vent system: winners and losers among closely related species. Mar. Ecol. Prog. Ser. 550, 121–134. https://doi.org/10.3354/meps1172.
Garilli, V., Rodolfo-Metalpa, R., Scuderi, D., Brusca, L., Parrinello, D., Rastrick, S.P.S., Foggo, A., Twitchett, R.J., Hall-Spencer, J.M., Milazzo, M., 2015. Physiological advantages of dwarfing in surviving extinctions in high-CO_2 oceans. Nat. Clim. Chang. 5, 678–682. https://doi.org/10.1038/nclimate2616.
Garrard, S.L., Gambi, M.C., Scipione, M.B., Patti, F.P., Lorenti, M., Zupo, V., Paterson, D. M., Buia, M.C., 2014. Indirect effects may buffer negative responses of seagrass invertebrate communities to ocean acidification. J. Exp. Mar. Biol. Ecol. 461, 31–38. https://doi.org/10.1016/j.jembe.2014.07.011.
Gerloff, T., Stieger, B., Hagenbuch, B., Madon, J., Landmann, L., Roth, J., Hofmann, A.F., Meier, P.J., 1998. The sister of P-glycoprotein represents the canalicular bile salt export pump of mammalian liver. J. Biol. Chem. 273, 10046–10050. https://doi.org/10.1074/jbc.273.16.10046.
Giangrande, A., Gambi, M.C., Micheli, F., Kroeker, K.J., 2014. Fabriciidae (Annelida, Sabellida) from a naturally acidified coastal system (Italy) with description of two new species. J. Mar. Biol. Assoc. UK 94 (7), 1417–1427. https://doi.org/10.1017/S0025315414000678.
Giangrande, A., Putignano, M., Licciano, M., Gambi, M.C., 2021. The Pandora's box: morphological diversity within the genus *Amphiglena* Claparède, 1864 (Sabellidae, Annelida) in the Mediterranean Sea with the description of nine new species. Zootaxa 4949 (2), 201–239. https://doi.org/10.11646/zootaxa.4949.2.1.
Goldberg, E.D., Bowen, V.T., Farrington, J.W., Harvey, G., Martin, J.H., Parker, P.L., Risebrough, R.W., Robertson, W., Schneider, E., Gamble, E., 1978. The mussel watch. Environ. Conserv. 5 (2), 101–125. https://doi.org/10.1017/S0376892900005555.
González-Delgado, S., Hernández, C., 2018. The importance of natural acidified systems in the study of ocean acidification: what have we learned? Adv. Mar. Biol. 80, 57–99. https://doi.org/10.1016/bs.amb.2018.08.001.

Goosen, N., Moolenaar, G.F., 2001. Role of ATP hydrolysis by UvrA and UvrB during nucleotide excision repair. Res. Microbiol. 152, 401–409. https://doi.org/10.1016/s0923-2508(01)01211-6.
Gottesman, M.M., Pastan, I., 1993. Biochemistry of multidrug resistance mediated by the multidrug transporter. Annu. Rev. Biochem. 62, 385–427. https://doi.org/10.1146/annurev.bi.62.070193.002125.
Gros, P., Croop, J., Housman, D., 1986. Mammalian multidrug resistance gene: complete cDNA sequence indicates strong homology to bacterial transport proteins. Cell 47, 371–380. https://doi.org/10.1016/0092-8674(86)90594-5.
Haimeur, A., Conseil, G., Deeley, R.G., Cole, S.P.C., 2004. The MRP-related and BCRP/ABCG2 multidrug resistance proteins: biology, substrate specificity and regulation. Curr. Drug Metab. 5 (1), 21–53. https://doi.org/10.2174/1389200043489199.
Halliwell, B., 1974. Superoxide dismutase, catalase and glutathione peroxidase: solutions to the problems of living with oxygen. New Phytol. 73 (6), 1075–1086. https://doi.org/10.1111/j.1469-8137.1974.tb02137.x.
Hall-Spencer, J., Rodolfo-Metalpa, R., Martin, S., Ransome, E., Fine, M., Turner, S.M., Rowley, S.J., Tedesco, D., Buia, M.-C., 2008. Volcanic carbon dioxide vents show ecosystem effects of ocean acidification. Nature 454, 96–99. https://doi.org/10.1038/nature07051.
Hamdoun, A.M., Cherr, G.N., Roepke, T.A., Epel, D., 2004. Activation of multidrug efflux transporter activity at fertilization in sea urchin embryos (*Strongylocentrotus purpuratus*). Dev. Biol. 276 (2), 452–462. https://doi.org/10.1016/j.ydbio.2004.09.013.
Hamdoun, A.M., Griffin, F.J., Cherr, G.N., 2002. Tolerance to biodegraded crude oil in marine invertebrate embryos and larvae is associated with expression of a multixenobiotic resistance transporter. Aquat. Toxicol. 61, 127–140. https://doi.org/10.1016/s0166-445x(02)00050-4.
Harvey, B.P., Gwynn-Jones, D., Moore, P.J., 2013. Meta-analysis reveals complex marine biological responses to the interactive effects of ocean acidification and warming. Ecol. Evol. 3 (4), 1016–1030. https://doi.org/10.1002/ece3.516.
Hendriks, I.E., Duarte, C.M., Álvarez, M., 2010. Vulnerability of marine biodiversity to ocean acidification: a meta-analysis. Estuar. Coast. Shelf Sci. 86 (2), 157–164. https://doi.org/10.1016/j.ecss.2009.11.022.
Hennige, S.J., Wolfram, U., Wickes, L., Murray, F., Roberts, J.M., Kamenos, N.A., Schofield, S., Groetsch, A., Spiesz, E.M., Aubin-Tam, M.-E., Etnoyer, P.J., 2020. Crumbling reefs and cold-water coral habitat loss in a future ocean: evidence of "coralporosis" as an indicator of habitat integrity. Front. Mar. Sci. 7, 668. https://doi.org/10.3389/fmars.2020.00668.
Hernández, C.A., Sangil, C., Hernández, J.C., 2016. A new CO_2 vent for the study of ocean acidification in the Atlantic. Mar. Pollut. Bull. 109 (1), 419–426. https://doi.org/10.1016/j.marpolbul.2016.05.040.
Higgins, C.F., 2007. Multiple molecular mechanisms for multidrug resistance transporters. Nature 446, 749–757. https://doi.org/10.1038/nature05630.
Hoegh-Guldberg, O., Mumby, P.J., Hooten, A.J., Steneck, R.S., Greenfield, P., Gomez, E., Harvell, C.D., Sale, P.F., Edwards, A.J., Caldeira, K., Knowlton, N., Eakin, C.M., Iglesias-Prieto, R., Muthiga, N., Bradbury, R.H., Dubi, A., Hatziolos, M.E., 2007. Coral reefs under rapid climate change and ocean acidification. Science 318 (5857), 1737–1742. https://doi.org/10.1126/science.1152509.
Homolya, L., Holló, Z., Germann, U.A., Pastan, I., Gottesman, M.M., Sarkadi, B., 1993. Fluorescent cellular indicators are extruded by the multidrug resistance protein. J. Biol. Chem. 268 (29), 21493–21496. https://doi.org/10.1016/S0021-9258(20)80566-3.
Huang, L., Zou, Y., Weng, H.-W., Li, H.-Y., Liu, J.-S., Yang, W.-D., 2015. Proteomic profile in *Perna viridis* after exposed to *Prorocentrum lima*, a dinoflagellate producing DSP toxins. Environ. Pollut. 196, 350e357 https://doi.org/10.1016/j.envpol.2014.10.019.
Hyde, S.C., Emsley, P., Hartshorn, M.J., Mimmack, M.M., Gileadi, U., Pearce, S.R., Gallagher, M.P., Gill, D.R., Hubbard, R.E., Higgins, C.F., 1990. Structural model of ATP-binding proteins associated with cystic fibrosis, multidrug resistance and bacterial transport. Nature 346, 362–365. https://doi.org/10.1038/346362a0.
Hyun, B., Kim, J.-M., Jang, P.-G., Jang, M.-C., Choi, K.-H., Lee, K., Yang, E.J., Noh, J.H., Shin, K., 2020. The effects of ocean acidification and warming on growth of a natural community of coastal phytoplankton. J. Mar. Sci. Eng. 8, 821. https://doi.org/10.3390/jmse8100821.
Igarashi, K., Kashiwagi, K., 1999. Polyamine transport in bacteria and yeast. Biochem. J. 344, 633–642. https://doi.org/10.1042/bj3440633.
IPCC, 2014. In: Pachauri, R.K., Meyer, L.A. (Eds.), Climate Change 2014: Synthesis Report. Contribution of Working Groups I, II and III to the Fifth Assessment Report of the Intergovernmental Panel on Climate Change. IPCC, Geneva, Switzerland, 151 pp.
Jeong, C.-B., Kim, H.-S., Kang, H.-M., Lee, J.-S., 2017. ATP-binding cassette (ABC) proteins in aquatic invertebrates: evolutionary significance and application in marine ecotoxicology. Aquat. Toxicol. 185, 29–39. https://doi.org/10.1016/j.aquatox.2017.01.013.
Jiang, L.-Q., Carter, B.R., Feely, R.A., Lauvset, S.K., Olsen, A., 2019. Surface Ocean pH and buffer capacity: past, present and future. Sci. Rep. 9, 18624. https://doi.org/10.1038/s41598-019-55039-4.
Jin, P., Zhang, J., Wan, J., Overmans, S., Gao, G., Ye, M., Dai, X., Zhao, J., Xiao, M., Xia, J., 2021. The combined effects of ocean acidification and heavy metals on marine organisms: a meta-analysis. Front. Mar. Sci. 8, 801889 https://doi.org/10.3389/fmars.2021.801889.
Joos, F., Spahni, R., 2008. Rates of change in natural and anthropogenic radiative forcing over the past 20,000 years. Proc. Natl. Acad. Sci. 105 (5), 1425–1430. https://doi.org/10.1073/pnas.0707386105.
Juliano, R.L., Ling, V., 1976. A surface glycoprotein modulating drug permeability in chinese hamster ovary cell mutants. Biochim. Biophys. Acta 455, 152–162. https://doi.org/10.1016/0005-2736(76)90160-7.
Jumars, P.A., Dorgan, K.M., Lindsay, S.M., 2015. Diet of worms emended: an update of polychaete feeding guilds appendix a family-by-family review. Annu. Rev. Mar. Sci. 7, 497–520. https://doi.org/10.1146/annurev-marine-010814-020007.
Kapsenberg, L., Cyronak, T., 2019. Ocean acidification refugia in variable environments. Glob. Chang. Biol. 25, 3201–3214. https://doi.org/10.1111/gcb.14730.
Kelaher, B.P., Mamo, L.T., Provost, E., Litchfield, S.G., Giles, A., Butcherine, P., 2022. Influence of ocean warming and acidification on habitat-forming coralline algae and their associated molluscan assemblages. Glob. Ecol. Conserv. 35, e02081 https://doi.org/10.1016/j.gecco.2022.e02081.
Kibria, G., Nugegoda, D., Rose, G., Haroon, A.K.Y., 2021. Climate change impacts on pollutants mobilization and interactive effects of climate change and pollutants on toxicity and bioaccumulation of pollutants in estuarine and marine biota and linkage to seafood security. Mar. Pollut. Bull. 167, 112364 https://doi.org/10.1016/j.marpolbul.2021.112364.
Kroeker, K.J., Kordas, R.L., Crim, R.N., Singh, G.G., 2010. Meta-analysis reveals negative yet variable effects of ocean acidification on marine organisms. Ecol. Lett. 13, 1419–1434. https://doi.org/10.1111/j.1461-0248.2010.01518.x.
Kroeker, K.J., Gambi, M.C., Micheli, F., 2013. Community dynamics and ecosystem simplification in a high-CO_2 ocean. Proc. Natl. Acad. Sci. U. S. A. 110 (31), 12721–12726. https://doi.org/10.1073/pnas.1216464110.
Kroeker, K.J., Kordas, R.L., Crim, R., Hendriks, I.E., Ramajo, L., Singh, G.S., Duarte, C.M., Gattuso, J.-P., 2013a. Impacts of ocean acidification on marine organisms: quantifying sensitivities and interaction with warming. Glob. Chang. Biol. 19, 1884–1896. https://doi.org/10.1111/gcb.12179.
Kroeker, K.J., Micheli, F., Gambi, M., 2013c. Ocean acidification causes ecosystem shifts via altered competitive interactions. Nat. Clim. Chang. 3, 156–159. https://doi.org/10.1038/nclimate1680.
Kurelec, B., 1992. The multixenobiotic resistance mechanism in aquatic organisms. Crit. Rev. Toxicol. 22 (1), 23–43. https://doi.org/10.3109/10408449209145320.
Landrigan, P.J., Stegeman, J.J., Fleming, L.E., Allemand, D., Anderson, D.M., Backer, L.C., Brucker-Davis, F., Chevalier, N., Corra, L., Czerucka, D., Bottein, M.-Y.D., Demeneix, B., Depledge, M., Deheyn, D.D., Dorman, C.J., Fénichel, P., Fisher, S., Gaill, F., Galgani, F., Gaze, W.H., Giuliano, L., Grandjean, P., Hahn, M.E., Hamdoun, A., Hess, P., Judson, B., Laborde, A., McGlade, J., Mu, J., Mustapha, A., Neira, M., Noble, R.T., Pedrotti, M.L., Reddy, C., Rocklöv, J., Scharler, U.M., Shanmugam, H., Taghian, G., van de Water, J.A.J.M., Vezzulli, L., Weihe, P., Zeka, A., Raps, H., Rampal, P., 2020. Human health and ocean pollution. Ann. Glob. Health 86 (1), 151. https://doi.org/10.5334/aogh.2831.
Leslie, E.M., Deeley, R.G., Cole, S.P.C., 2005. Multidrug resistance proteins: role of P-glycoprotein, MRP1, MRP2, and BCRP (ABCG2) in tissue defense. Toxicol. Appl. Pharmacol. 204, 216–237. https://doi.org/10.1016/j.taap.2004.10.012.
Li, X.Z., Nikaido, H., 2004. Efflux-mediated drug resistance in bacteria. Drugs 64 (2), 159–204. https://doi.org/10.2165/00003495-200464020-00004.
Lim, E.G., Harley, C.D.G., 2018. Caprellid amphipods (*Caprella* spp.) are vulnerable to both physiological and habitat-mediated effects of ocean acidification. PeerJ 6, e5327. https://doi.org/10.7717/peerj.5327.
Linton, K.J., 2015. Lipid flopping in the liver. Biochem. Soc. Trans. 43, 1003–1010. https://doi.org/10.1042/BST20150132.
Litman, T., Druley, T.E., Stein, W.D., Bates, S.E., 2001. From MDR to MXR: new understanding of multidrug resistance systems, their properties and clinical significance. Cell. Mol. Life Sci. 58, 931–959. https://doi.org/10.1007/PL00000912.
Lončar, J., Popović, M., Zaja, R., Smital, T., 2010. Gene expression analysis of the ABC efflux transporters in rainbow trout (*Oncorhynchus mykiss*). Comp. Biochem. Physiol. C 151, 209–215. https://doi.org/10.1016/j.cbpc.2009.10.009.
Lucey, N.M., Lombardi, C., De March, L., Schulze, A., Gambi, M.C., Calosi, P., 2015. To brood or not to brood. Are marine organisms that protect their offspring more resilient to ocean acidification? Sci. Rep. 5, 12009. https://doi.org/10.1038/srep12009.
Luckenbach, T., Epel, D., 2008. ABCB- and ABCC-type transporters confer multixenobiotic resistance and form an environment-tissue barrier in bivalve gills. Am. J. Physiol. Regul. Integr. Comp. Physiol. 294, R1919–R1929. https://doi.org/10.1152/ajpregu.00563.2007.
Maibam, C., Fink, P., Romano, G., Buia, M.C., Butera, E., Zupo, V., 2015. *Centropages typicus* (Crustacea, Copepoda) reacts to volatile compounds produced by planktonic algae. Mar. Ecol. https://doi.org/10.1111/maec.12254. ISSN 0173-9565.
Maibam, C., Fink, P., Romano, G., Buia, M.C., Zupo, V., 2012. Influence of seawater acidification on the chemosensory abilities and volatile organic compound detection by the planktonic copepod *Centropages typicus*. In: Presented at: 50th ECSA Conference, 3-7 June 2012, Venice, Italy.
Matsuhashi, A., Tahara, H., Ito, Y., Uchiyama, J., Ogawa, S., Ohta, H., 2015. Slr 2019, lipid a transporter homolog, is essential for acidic tolerance in *Synechocystis* sp. PCC6803. Photosynth. Res. 125, 267–277. https://doi.org/10.1007/s11120-015-0129-6.
McDevitt, C.A., Callaghan, R., 2007. How can we best use structural information on P-glycoprotein to design inhibitors? Pharmacol. Ther. 113 (2), 429–441. https://doi.org/10.1016/j.pharmthera.2006.10.003.
McFadzen, I., Eufemia, N., Heath, C., Epel, D., Moore, M., Lowe, D., 2000. Multidrug resistance in the embryos and larvae of the mussel *Mytilus edulis*. Mar. Environ. Res. 50, 319–323. https://doi.org/10.1016/s0141-1136(00)00057-x.
Mecca, S., Casoli, E., Ardizzone, G., Gambi, M.C., 2020. Effects of ocean acidification on phenology and epiphytes of the seagrass Posidonia oceanica: evidences from two CO_2 vent systems. Mediterr. Mar. Sci. 21 (1), 70–83. https://doi.org/10.12681/mms.20795.
Migliaccio, O., Pinsino, A., Maffioli, E., Smith, A.M., Agnisola, C., Matranga, V., Nonnis, S., Tedeschi, G., Byrne, M., Gambi, M.C., Palumbo, A., 2019. Living in future ocean acidification, physiological adaptive responses of the immune system of sea

urchins resident at a CO_2 vent system. Sci. Total Environ. 672, 938–950. https://doi.org/10.1016/j.scitotenv.2019.04.005.
Moya, A., Huisman, L., Ball, E.E., Hayward, D.C., Grasso, L.C., Chua, C.M., Woo, H.N., Gattuso, J.-P., Fore, S., Miller, D.J., 2012. Whole transcriptome analysis of the coral *Acropora millepora* reveals complex responses to CO_2-driven acidification during the initiation of calcification. Mol. Ecol. 21, 2440–2454. https://doi.org/10.1111/j.1365-294X.2012.05554.x.
Muñoz-Lasso, D.C., Romá-Mateo, C., Pallardó, F.V., Gonzalez-Cabo, P., 2020. Much more than a scaffold: cytoskeletal proteins in neurological disorders. Cells 9 (2), 358. https://doi.org/10.3390/cells9020358.
Muralisankar, T., Kalaivania, P., Thangala, S.H., Santhanam, P., 2021. Growth, biochemical, antioxidants, metabolic enzymes and hemocytes population of the shrimp *Litopenaeus vannamei* exposed to acidified seawater. Comp. Biochem. Physiol. 239 (C), 108843 https://doi.org/10.1016/j.cbpc.2020.108843.
Mutalipassi, M., Mazzella, V., Zupo, V., 2019. Ocean acidification influences plant-animal interactions: the effect of *Cocconeis scutellum* parva on the sex reversal of *Hippolyte inermis*. PLoS ONE 14 (6), e0218238. https://doi.org/10.1371/journal.pone.0218238.
Mutalipassi, M., Fink, P., Maibam, C., Porzio, L., Buia, M.C., Gambi, M.C., Patti, F.P., Scipione, M.B., Lorenti, M., Zupo, V., 2020. Ocean acidification alters the responses of invertebrates to wound-activated infochemicals produced by epiphytes of the seagrass *Posidonia oceanica*. J. Exp. Mar. Biol. Ecol. 530–531, 151435 https://doi.org/10.1016/j.jembe.2020.151435.
Mutalipassi, M., Mazzella, V., Schott, M., Fink, P., Glaviano, F., Porzio, L., Lorenti, M., Buia, M.C., von Elert, E., Zupo, V., 2022. Ocean acidification affects volatile infochemicals production and perception in fauna and flora associated with *Posidonia oceanica* (L.) Delile. Front. Mar. Sci. 9, 809702 https://doi.org/10.3389/fmars.2022.809702.
Nicolaou, M., Andress, E.J., Zolnerciks, J.K., Dixon, P.H., Williamson, C., Linton, K.J., 2012. Canalicular ABC transporters and liver disease. J. Pathol. 226, 300–315. https://doi.org/10.1002/path.3019.
Nilsson, K.S., Wallberge, A., Jondelius, U., 2011. New species of acoela from the Mediterranean, the Red Sea, and South Pacific. Zootaxa 2867, 1–31. https://doi.org/10.11646/zootaxa.2867.1.1.
Olsgard, F., Brattegard, T., Holthe, T., 2003. Polychaetes as surrogates for marine biodiversity: lower taxonomic resolution and indicator groups. Biodivers. Conserv. 12, 1033–1049. https://doi.org/10.1023/A:1022800405253.
Orr, J.C., Fabry, V.J., Aumont, O., Bopp, L., Doney, S.C., Feely, R.A., Gnanadesikan, A., Gruber, N., Ishida, A., Joos, F., Key, R.M., Lindsay, K., Maier-Reimer, E., Matear, R., Monfray, P., Mouchet, A., Najjar, R.G., Plattner, G.-K., Rodgers, K.B., Sabine, C.L., Sarmiento, J.L., Schlitzer, R., Slater, R.D., Totterdell, I.J., Weirig, M.-F., Yamanaka, Y., Yool, A., 2005. Anthropogenic Ocean acidification over the twenty-first century and its impact on calcifying organisms. Nature 437, 681–686. https://doi.org/10.1038/nature04095.
Ponder, W.F., Lindberg, D.R. (Eds.), 2008. Phylogeny and evolution of the Mollusca. University of California Press, Berkeley.
Popovic, M., Zaja, R., Loncar, J., Smital, T., 2010. A novel ABC transporter: the first insight into zebrafish (*Danio rerio*) ABCH1. Mar. Environ. Res. 69, S11–S13. https://doi.org/10.1016/j.marenvres.2009.10.016.
Porzio, L., Buia, M.C., Hall-Spencer, J.M., 2011. Effects of ocean acidification on macroalgal communities. J. Exp. Mar. Biol. Ecol. 400, 278–287. https://doi.org/10.1016/j.jembe.2011.02.011.
Rastrick, S.S.P., Graham, H., Azetsu-Scott, K., Calosi, P., Chierici, M., Fransson, A., Hop, H., Hall-Spencer, J., Milazzo, M., Thor, P., Kutti, T., 2018. Using natural analogues to investigate the effects of climate change and ocean acidification on northern ecosystems. ICES J. Mar. Sci. 75 (7), 2299–2311. https://doi.org/10.1093/icesjms/fsy128.
Raven, J., Caldeira, K., Elderfield, H., Hoegh-Guldberg, O., Liss, P., Riebesell, U., Shepherd, J., Turley, C., Watson, A., 2005. Ocean acidification due to increasing atmospheric carbon dioxide. The Royal Society, London, UK.
Rea, P.A., 2007. Plant ATP-binding cassette transporters. Annu. Rev. Plant Biol. 58, 347–375. https://doi.org/10.1146/annurev.arplant.57.032905.105406.
Ren, J., Chung-Davidson, Y.-W., Yeh, C.-Y., Scott, C., Brown, T., Li, W., 2015. Genome-wide analysis of the ATP-binding cassette (ABC) transporter gene family in sea lamprey and japanese lamprey jianfeng. BMC Genomics 16, 436. https://doi.org/10.1186/s12864-015-1677-z.
Ricevuto, E., Lorenti, M., Patti, F.P., Scipione, M.B., Gambi, M.C., 2012. Temporal trends of benthic invertebrate settlement along a gradient of ocean acidification at natural CO_2 vents (Tyrrhenian Sea). Biol. Mar. Mediterr. 19 (1), 49–52.
Ricevuto, E., Kroeker, F., Ferrigno, F., Micheli, F., Gambi, M.C., 2014. Spatio-temporal variability of polychaete colonization at volcanic CO_2 vents indicates high tolerance to ocean acidification. Mar. Biol. 161, 2909–2919. https://doi.org/10.1007/s00227-014-2555-y.
Ricevuto, E., Benedetti, M., Regoli, F., Spicer, J.I., Gambi, M.C., 2015. Antioxidant capacity of polychaetes occurring at a natural CO_2 vent system: results of an in situ reciprocal transplant experiment. Mar. Environ. Res. 112, 44–51. https://doi.org/10.1016/j.marenvres.2015.09.005.
Rodolfo-Metalpa, R., Houlbrèque, F., Tambutté, É., Boisson, F., Baggini, C., Patti, F.P., Jeffree, R., Fine, M., Foggo, A., Gattuso, J.-P., Hall-Spencer, J.M., 2011. Coral and mollusc resistance to ocean acidification adversely affected by warming. Nat. Clim. Chang. 1, 308–312. https://doi.org/10.1038/nclimate1200.
Roepke, T.A., Hamdoun, A.M., Cherr, G.N., 2006. Increase in multidrug transport activity is associated with oocyte maturation in sea stars. Develop. Growth Differ. 48, 559–573. https://doi.org/10.1111/j.1440-169X.2006.00893.x.
Roninson, I.B., Abelson, A.T., Housman, D., Howell, N., Varshavsky, A., 1984. Amplification of specific DNA sequences correlates with multi-drug resistance in Chinese hamster cells. Nature 309, 626–628. https://doi.org/10.1038/309626a0.
Saha, M., Berdalet, E., Carotenuto, Y., Fink, P., Harder, T., John, U., Not, F., Pohnert, G., Potin, P., Selander, E., Vyverman, W., Wichard, T., Zupo, V., Steinke, M., 2019. Babylonian towers in a blue world - using chemical language to shape future marine health. Front. Ecol. Environ. 17 (9), 530–537. https://doi.org/10.1002/fee.2113.
Sangari, F.J., Cayón, A.M., Seoane, A., García-Lobo, J.M., 2010. *Brucella abortus* ure2 region contains an acid-activated urea transporter and a nickel transport system. BMC Microbiol. 10, 107. https://doi.org/10.1186/1471-2180-10-107.
Santana-Casiano, J.M., Fraile-Nuez, E., González-Dávila, M., Baker, E.T., Resing, J.A., Walker, S.L., 2016. Significant discharge of CO2 from hydrothermalism associated with the submarine volcano of El Hierro Island. Sci. Rep. 6, 25686. https://doi.org/10.1038/srep25686.
Sauerborn, R., Polancec, D.S., Zaja, R., Smital, T., 2004. Identification of the multidrug resistance-associated protein (mrp) related gene in red mullet (*Mullus barbatus*). Mar. Environ. Res. 58 (2–5), 199–204. https://doi.org/10.1016/j.marenvres.2004.03.120.
SawKatare, E.E.L., Rawal, S., Pearson, J., Schwenke, D., Kakinuma, Y., Fronius, M., Katare, R., 2020. Diabetes induced dysregulation of cardiac non-neuronal cholinergic system impairs heart metabolism. J. Mol. Cell. Cardiol. 140, 14. https://doi.org/10.1016/j.yjmcc.2019.11.031.
Schinkel, A.H., Smit, J.J.M., Vantellingen, O., Beijnen, J.H., Wagenaar, E., Vandeemter, L., Mol, C., Vandervalk, M.A., Robanusmaandag, E.C., Teriele, H.P.J., Berns, A.J.M., Borst, P., 1994. Disruption of the mouse mdr1a P-glycoprotein gene leads to a deficiency in the blood-brain barrier and to increased sensitivity to drugs. Cell 77, 491–502. https://doi.org/10.1016/0092-8674(94)90212-7.
Shamberger, K.E.F., Cohen, A.L., Golbuu, Y., McCorkle, D.C., Lentz, S.J., Barkley, H.C., 2014. Diverse coral communities in naturally acidified waters of a Western Pacific reef. Geophys. Res. Lett. 41, 499–504. https://doi.org/10.1002/2013GL058489.
Shumway, S.E., Parsons, G.J., 2006. In: Shumway, S.E., Parsons, G.J. (Eds.), Scallops: Biology, Ecology and Aquaculture. Elsevier Science.
Shvarev, D., Maldener, I., 2020. The HlyD-like membrane fusion protein All5304 is essential for acid stress survival of the filamentous cyanobacterium *Anabaena* sp. PCC 7120. FEMS Microbiol. Lett. 367 (15) https://doi.org/10.1093/femsle/fnaa108.
Snezhkina, A.V., Kudryavtseva, A.V., Kardymon, O.L., Savvateeva, M.V., Melnikova, N. V., Krasnov, G.S., Dmitriev, A.A., 2019. ROS generation and antioxidant defense systems in normal and malignant cells. Oxidative Med. Cell. Longev. 5, 6175804 https://doi.org/10.1155/2019/6175804.
Spilling, K., Paul, A.J., Virkkala, N., Hastings, T., Lischka, S., Stuhr, A., Bermúdez, R., Czerny, J., Boxhammer, T., Schulz, K.G., Ludwig, A., Riebesell, U., 2016. Ocean acidification decreases plankton respiration: evidence from a mesocosm experiment. Biogeosciences 13, 4707–4719. https://doi.org/10.5194/bg-13-4707-2016.
Sun, J., Zhang, Y., Xu, T., Zhang, Y., Mu, H., Zhang, Y., Lan, Y., Fields, C.J., Ho Lam Hui, J., Zhang, W., Li, R., Nong, W., Ka Man Cheung, F., Qiu, J.-W., Qian, P.-Y., 2017. Adaptation to deep-sea chemosynthetic environments as revealed by mussel genomes. Nat. Ecol. Evol. 1, 0121 https://doi.org/10.1038/s41559-017-0121.
Sunday, J.M., Crim, R.N., Harley, C.D.G., Hart, M.W., 2011. Quantifying rates of evolutionary adaptation in response to ocean acidification. PloS One 6 (8), e22881. https://doi.org/10.1371/journal.pone.0022881.
Sunday, J.M., Calosi, P., Dupont, S., Munday, P.L., Stillman, J.H., Reusch, T.B., 2013. Evolution in an acidifying ocean. Trends Ecol. Evol. 29 (2), 117–125. https://doi.org/10.1016/j.tree.2013.11.001.
Tahara, H., Uchiyama, J., Yoshihara, T., Matsumoto, K., Ohta, H., 2012. Role of slr 1045 in environmental stress tolerance and lipid transport in the cyanobacterium *Synechocystis* sp. PCC6803. Biochim. Biophys. Acta 1817, 1360–1366.
Tahara, H., Matsuhashi, A., Uchiyama, J., Ogawa, S., Ohta, H., 2015. Sll0751 and Sll1041 are involved in acid stress tolerance in *Synechocystis* sp. PCC 6803. Photosynth. Res. 125, 233–242. https://doi.org/10.1007/s11120-015-0153-6.
Takahashi, T., Sutherland, S.C., Chipman, D.W., Goddard, J.G., Ho, C., Newberger, T., Sweeney, C., Munro, D.R., 2014. Climatological distributions of pH, pCO_2, total CO_2, alkalinity, and $CaCO_3$ saturation in the global surface ocean, and temporal changes at selected locations. Mar. Chem. 164, 95–125. https://doi.org/10.1016/j.marchem.2014.06.004.
Tanaka, J., Trianto, A., Musman, M., Issa, H.H., Ohtani, I.I., Ichiba, T., Higa, T., Yoshida, W.Y., Scheuerc, P.J., 2002. New polyoxygenated steroids exhibiting reversal of multidrug resistance from the gorgonian *Isis hippuris*. Tetrahedron 58, 6259–6266. https://doi.org/10.1016/S0040-4020(02)00625-7.
Teixidó, N., Gambi, M.C., Parravacini, V., Kroeker, K., Micheli, F., Villéger, S., Ballesteros, E., 2018. Functional biodiversity loss along natural CO_2 gradients. Nat. Commun. 9, 5149. https://doi.org/10.1038/s41467-018-07592-1.
Tutundjian, R., Cachot, J., Leboulenger, F., Minier, C., 2002. Genetic and immunological characterisation of a multixenobiotic resistance system in the turbot (*Scophthalmus maximus*). Comp. Biochem. Physiol. B 132, 463–471. https://doi.org/10.1016/S1096-4959(02)00058-1.
Uchiyama, J., Itagaki, A., Ishikawa, H., Tanaka, Y., Kohga, H., Nakahara, A., Imaida, A., Tahara, H., Ohta, H., 2019. Characterization of ABC transporter genes, sll1180, sll1181, and slr1270, involved in acid stress tolerance of *Synechocystis* sp. PCC 6803. Photosynth. Res. 139, 325–335. https://doi.org/10.1007/s11120-018-0548-2.
Valvassori, G., Benedetti, M., Regoli, F., Gambi, M.C., 2019. Antioxidant efficiency of *Platynereis* spp. (Annelida, Nereididae) under different pH conditions at a CO_2 vent's system. J. Mar. Biol. 2019, 8415916 https://doi.org/10.1155/2019/8415916.
Vidal-Dupiol, J., Zoccola, D., Tambutté, E., Grunau, C., Cosseau, C., Smith, K.M., Freitag, M., Dheilly, N.M., Allemand, D., Tambutté, S., 2013. Genes related to ion-transport and energy production are upregulated in response to CO_2-driven pH

decrease in corals: new insights from transcriptome analysis. PLoS ONE 8 (3), e58652. https://doi.org/10.1371/journal.pone.0058652.

Vizzini, S., Martínez-Crego, B., Andolina, C., Massa-Gallucci, A., Connell, S.D., Gambi, M. C., 2017. Ocean acidification as a driver of community simplification via the collapse of higher-order and rise of lower-order consumers. Sci. Rep. 7, 4018. https://doi.org/10.1038/s41598-017-03802-w.

Wäge, J., Lerebours, A., Hardege, J.D., Rotchell, J.M., 2016. Exposure to low pH induces molecular level changes in the marine worm, *Platynereis dumerilii*. Ecotoxicol. Environ. Saf. 124, 105–110. https://doi.org/10.1016/j.ecoenv.2015.10.008.

Wang, X., Wang, M., Jia, Z., Wang, H., Jiang, S., Chen, H., Wang, L., Song, L., 2016. Ocean acidification stimulates alkali signal pathway: a bicarbonate sensing soluble adenylyl cyclase from oyster *Crassostrea gigas* mediates physiological changes induced by CO_2 exposure. Aquat. Toxicol. 181, 124–135. https://doi.org/10.1016/j.aquatox.2016.11.002.

Wang, W., Wang, M., Wang, W., Liu, Z., Xu, J., Jia, Z., Chena, H., Qiu, L., Lv, Z., Wang, L., Song, L., 2020. Transcriptional changes of Pacific oyster *Crassostrea gigas* reveal essential role of calcium signal pathway in response to CO_2-driven acidification. Sci. Total Environ. 741, 140177 https://doi.org/10.1016/j.scitotenv.2020.140177.

Wilson, D.F., Matschinsky, F.M., 2021. Metabolic homeostasis in life as we know it: its origin and thermodynamic basis. Front. Physiol. 12, 658997 https://doi.org/10.3389/fphys.2021.658997.

Xing, Q., Liao, H., Peng, C., Zheng, G., Yang, Z., Wang, J., Lu, W., Huang, X., Bao, Z., 2021. Identification, characterization and expression analyses of cholinesterases genes in yesso scallop (*Patinopecten yessoensis*) reveal molecular function allocation in responses to ocean acidification. Aquat. Toxicol. 231, 105736 https://doi.org/10.1016/j.aquatox.2020.105736.

Zeng, X., Chen, X., Zhuang, J., 2015. The positive relationship between ocean acidification and pollution. Mar. Pollut. Bull. 91, 14–21. https://doi.org/10.1016/j.marpolbul.2014.12.001.

Zhu, Z., Yang, Y., Yang, P., Wu, Z., Zhang, J., Du, G., 2019. Enhanced acid-stress tolerance in *Lactococcus lactis* NZ9000 by overexpression of ABC transporters. Microb. Cell Factories 18, 136. https://doi.org/10.1186/s12934-019-1188-8.

Zhu, X., Liao, H., Yang, Z., Penga, C., Lu, W., Xing, Q., Huang, X., Hu, J., Bao, Z., 2020. Genome-wide identification, characterization of RLR genes in yesso scallop (*Patinopecten yessoensis*) and functional regulations in responses to ocean acidification. Fish Shellfish Immunol. 98, 488–498. https://doi.org/10.1016/j.fsi.2020.01.036.

Zucchi, S., Corsi, I., Luckenbach, T., Bard, S.M., Regoli, M., Focardi, S., 2010. Identification of five partial ABC genes in the liver of the Antarctic fish *Trematomus bernacchii* and sensitivity of ABCB1 and ABCC2 to cd exposure. Environ. Pollut. 158, 2746e2756 https://doi.org/10.1016/j.envpol.2010.04.012.

Zunino, S., Canu, D.M., Zupo, V., Solidoro, C., 2019. Direct and indirect impacts of marine acidification on the ecosystem services provided by coralligenous reefs and seagrass systems. Glob. Ecol. Conserv. 18, e00625 https://doi.org/10.1016/j.gecco.2019.e00625.

Zupo, V., Viel, T., 2020. Ocean acidification alters the composition of decapod crustacean communities associated to *Posidonia oceanica* beds. Bulletin of Regional Natural History (BORNH). http://www.societanaturalistinapoli.it/images/bornh/zupo_e_viel.pdf.

Zupo, V., Maibam, C., Buia, M.C., Gambi, M.C., Scipione, M.B., Lorenti, M., Patti, F., Fink, P., 2015. Chemoreception of the seagrass *Posidonia oceanica* infochemicals by benthic invertebrates is altered by seawater acidification. J. Chem. Ecol. 41 (8), 766–779. https://doi.org/10.1007/s10886-015-0610-x.