Review

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Review

Antioxidant System in Extremophile Marine Fish Species

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Abstract: Living in extreme environments, marine organisms face constant exposure to a range of stressors, such as high radiation levels, fluctuations in temperature, and oxidative stress. Understanding extremophile fishes is crucial because it gives us valuable insights into the biochemical, physiological, and developmental processes that govern life, by observing how they operate under natural stressors. Among the most fascinating adaptations is the existence of specialised enzymes and compounds that function as potent antioxidants, successfully counteracting reactive oxygen species' deleterious effects. In this review, we analysed the findings from several studies on Antarctic and deep-sea fish species, while highlighting the environmental stressors effects toward the antioxidant system. The antioxidant defences of the considered extremophile fishes have been extensively studied, but there is still much to learn to fully understand this complex system, while the relative research is still ongoing. Consequently, we are properly anticipating further advancements over the next few years about our understanding of crucial physiological processes that support cell survival.

Keywords: oxidative stress; Antarctic fish; deep sea-fish

1. Introduction

Marine organisms living in extreme environments are constantly exposed to various stressors, including high radiation levels, temperature fluctuations, and oxidative stress [1]. Recent studies have revealed the fascinating adaptations and antioxidant systems marine organisms from extreme environments have developed to cope with these challenges [2]. One of the most intriguing findings is the presence of unique enzymes and compounds that act as powerful antioxidants, effectively neutralizing the harmful effects of reactive oxygen species (ROS) [3].

For instance, deep-sea marine invertebrates possess a robust network of antioxidant enzymes, such as superoxide dismutase (SOD) and catalase (CAT), which play a crucial role in scavenging ROS generated by high levels of radiation in their habitat [4]. Furthermore, specialized antioxidant compounds, such as carotenoids and polyphenols, were also identified, demonstrating the multifaceted nature of antioxidant defense in these organisms [5].

Furthermore, in Antarctic fish species, the heat shock proteins have been maintained despite the absence of environmental heat stress for at least 2.5 million years [6], while other mechanisms have been created to counteract the detrimental effects of both high temperatures and oxidative stress [7].

These findings expand our understanding of antioxidant systems in marine organisms and hold potential implications for various fields, including biotechnology and medicine. Further research in this area could inspire the development of novel antioxidant-based strategies for mitigating oxidative stress-related diseases and enhancing the stability of biotechnological products [8].

2. Oxidative Stress and Antioxidant Defense

O_2, a vital molecule for the existence of many organisms on Earth, plays a pivotal role in all oxidation reactions that define aerobic cell metabolism. It serves as the ultimate acceptor in the electron transport chain, leading to the production of ATP at the mitochondrial level. In these processes, O_2 is reduced to water. However, some electrons can directly react with O_2, forming reduction intermediates known as reactive oxygen species (ROS) and nitrogen species and include superoxide radicals ($\bullet O_2^-$), hydroxyl radical ($\bullet OH$), singlet oxygen, hydrogen peroxide (H_2O_2), peroxynitrite ($ONOO^-$), and many others [9]. It has been estimated that about 3% of the O_2 utilised by the cell is improperly converted into ROS, either through the activation of the mitochondrial electron transporter chains, spontaneous oxidation of reduced flavinins, hydroquinones, catecholamines and ferredoxins, or by the action of enzymes like xanthine oxidase, aldehyde oxidase and flavin dehydrogenase [10]. This formation rate can significantly increase under various physiological and stressful conditions such as physical activity, immune response, ageing, disease and exposure to xenobiotics [11–13].

ROS can be very harmful to organisms, and their formation must be kept under homeostatic control. Indeed, they can oxidise biological macromolecules such as lipids, proteins and DNA, leading to membrane alterations, inactivation of enzymes and receptors, modification of cytoskeleton proteins and damage to the genome. In other cases, their production can be beneficial, such as in macrophages and neutrophil granulocytes that produce H_2O_2 to eliminate pathogenic microorganisms in phagocytosis and bacteriolysis or when they control intracellular signalling pathways [14]. When the cellular concentration of ROS exceeds the cell's antioxidant capacity, the intracellular redox balance is altered, and a condition called oxidative stress is established [15]. Cells have evolved highly effective antioxidant defence systems, consisting of enzymatic and non-enzymatic components, capable of neutralising and blocking damage propagation [16].

Enzyme-type antioxidants include proteins such as SOD, CAT, glutathione peroxidase (GPx), glutathione S-transferase (GST), peroxiredoxin (Prdx), aldocheto-reductase and aldehyde dehydrogenase. These enzymes, as a whole, represent a first line against ROS but do not guarantee complete coverage from the risk of oxidative stress because some compounds generated by their reactions are still reactive and potentially cytotoxic, such as H_2O_2 produced by SOD. Therefore, a joint and coordinated action of the different enzymatic components is necessary to prevent further intracellular damage.

SODs are ubiquitous antioxidant enzymes that protect cells from the damaging action of $\bullet O_2^-$ by catalysing its dismutation into O_2 and H_2O_2. These enzymes also prevent the formation of $ONOO^-$, a strongly oxidising non-radiative ROS resulting from the interaction between nitric oxide and $\bullet O_2^-$ [17,18]. In animals, there are three known types of SODs: manganese SOD (Mn SOD or SOD2), which is localised in the mitochondrial matrix, and two Cu,Zn SODs, namely intracellular SOD and extracellular SOD (EC SOD or SOD3) [19,20].

CAT is an enzyme found mainly in peroxisomes. Its two enzymatic activities depend on the H_2O_2 concentration. If the H_2O_2 concentration is high, CAT acts catalytically, i.e., it removes H_2O_2 to form H_2O and O_2 (catalytic reaction). However, at a low H_2O_2 concentration and in the presence of a suitable hydrogen donor, e.g., ethanol, methanol, phenol, and others, CAT acts peroxidically, removing H_2O_2 but oxidising its substrate (peroxidic reaction) [21].

GPx is a family of enzymes, some containing selenium, capable of reducing organic and inorganic hydroperoxides to the corresponding hydroxyl compounds using glutathione (GSH) or other reducing equivalents [22,23]. The family of glutathione peroxidases comprises more than hundreds of members spread over all domains of life [24]. In vertebrates, up to 8 distinct GPxs were identified. Most of them are selenoproteins (mammalian GPx-1, GPx-2, GPx-3, GPx-4, and human GPx-6), while, in the remaining isoforms, the selenocysteine residue (Sec) is replaced by cysteine [25].

Prdx is a family of enzymes with peroxidase activity in various organisms, from prokaryotes to eukaryotes, including yeasts, plants, and animals. There are up to six known isoforms of peroxiredoxins, categorised into three families: typical 2-Cys, atypical 2-Cys, and 1-Cys. These families differ in structural and mechanistic characteristics [26]. The action of Prdx is mainly aimed at reducing H_2O_2, peroxynitrite, and a wide range of organic peroxides in alcohol and water [27,28].

The class of non-enzymatic antioxidants consists of low molecular weight molecules rich in thiol groups, such as metallothioneins (MTs) and GSH, that are biosynthesised by the cell [29,30]. In addition to being a substrate for GPx and GST, the GSH can act directly as a scavenger of ROS during the detoxification processes of H_2O_2 and lipid hydroperoxides. Then other compounds are usually acquired through the diet, such as ubiquinol, provitamin A, vitamins C, E, B6, B9, B12 and P, selenium, β-carotenoids and polyphenols. These molecules are mostly considered chain-breaking antioxidants as they interrupt the autocatalytic action of radical reactions, blocking the propagation of oxidative damage [31,32].

3. Antioxidants in Extreme Marine Environments

Extreme environments, such as high salinity or extreme temperatures, present unique challenges for aquatic organisms. However, certain species of extremophile fish have adapted to thrive in these harsh conditions [33].

Extremophile fishes are important because understanding how they function under natural stressors provides fundamental insight into the biochemical, physiological, and developmental processes that govern life. Consequently, it provides opportunities for translational science. For example, blind Mexican cavefish have already been a model for the eye to study development and degeneration [34]. The annual killifish of the genus *Nothobranchius* has emerged as a study system for age-related research [35]. Additionally, fish adapted to sulfide and anthropogenically toxic environments may provide insights into biomedical applications related to disrupting H_2S homeostasis [36] and tissue processing of xenobiotics [37]. The list of extremophile fish species would be huge, but we will focus on marine species from the Earth's pole and the deep sea or ocean.

These extremophile fishes have evolved special physiological and behavioral adaptations that allow them to survive and even thrive in environments where other species struggle to survive. Some examples of extremophile fishes include the icefish of Antarctica, which have unique antifreeze proteins in their blood [20], and the deep-sea anglerfish, which can withstand the extreme pressure and darkness of the deep oceans [38]. These remarkable creatures continue to fascinate and inspire researchers as they uncover the secrets of their incredible adaptations [39]. The diversity and unique adaptations of extremophile fishes provide insights into the limits of life on Earth and have broader implications [40]. They can provide valuable information and potential solutions for human-induced environmental challenges, such as understanding how organisms cope with pollution or global warming [41].

3.1. Antarctic Fish

Around 40 million years ago, Antarctica separated from the other continents and became one of Earth's most unique and extraordinary places. The Notothenioidei, a dominant fish sub-order in the Southern Ocean, have evolved in this distinct environment over millions of years, adapting to consistently cold (-1.8°C) and oxygen-rich waters, which has profoundly influenced their metabolic processes [42]. Within this suborder, the Channichthyidae family is notable for its adult members lacking haemoglobin [43] and, in some species, such as *Chaenocephalus aceratus,* also lack cardiac myoglobin [44].

Antarctic fish's evolutionary path has resulted in unique adaptations to extreme cold, including slower metabolic and growth rates, delayed reproductive maturity, longer lifespans, and strict stenothermy [42]. Additional adaptations include the accumulation of lipid droplets in the cytosol, a higher proportion of polyunsaturated fatty acids (PUFA) in cell membranes, distinctive modifications in their cardiovascular system, increased mitochondrial surface area and density, high plasma osmolarity and the presence of antifreeze glycoproteins [45,46]. These adaptations have enabled Antarctic fish to occupy various ecological niches, making them a significant Southern Ocean ecosystem component.

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However, the high levels of membrane PUFA in cold-adapted fish make them more susceptible to oxidative damage. PUFA is particularly vulnerable to ROS, and the half-life of ROS is extended at low temperatures, increasing the risk of oxidative damage and lipid peroxidation (LPO) in polar species [47]. Additionally, the saturation of Antarctic waters and consequently the body fluids of Antarctic fish with oxygen, due to the increased solubility of O_2 at lower temperatures, results in higher rates of cellular ROS formation [47–49].

Therefore, it is expected that Antarctic fish have developed highly effective and specialised antioxidant defence systems to counteract the increased ROS formation in cold environments, enabling them to thrive in the harsh Antarctic conditions [47,50].

The evolutionary history of Antarctic fish illustrates how life can adapt to extreme conditions over millions of years, highlighting the need for further research into the adaptation mechanisms related to oxidative metabolism in extreme environments [51]. Cells possess a complex antioxidant system consisting of enzymatic and non-enzymatic defences, interacting in a sophisticated network and protecting biological macromolecules from oxidative damage [52].

3.1.1. Enzymatic Antioxidant System

Primary antioxidant defences in Antarctic fish include SODs. One of the earliest studies investigating SOD activity in the liver of different Antarctic fish species found significantly higher activity (seven-fold) in red-blooded fish compared to white-blooded fish [53,54]. Freshwater fish exhibited intermediate SOD activity, about 2.5 times higher than in white-blooded fish but 2.5 times lower than in red-blooded fish. These differences are likely attributed to variations in oxygen transport mechanisms. These initial findings highlighted the critical role of superoxide dismutase as a primary defence against uncontrolled oxidation in cells [54], especially in organs with higher metabolic activity, such as the heart. It is precisely at the level of this organ that the most significant differences emerge between different Antarctic fish species concerning SOD expression, primarily related to greater or lesser locomotor activity [50].

Due to the high production of H_2O_2 by SODs, CAT is essential for scavenging this reactive oxygen species. However, CAT activity levels are generally low across all studied Antarctic fish species, approximately two-fold lower than in freshwater species [54]. Further research has confirmed the low basal activity of CAT in Antarctic fish compared to temperate species. For instance, higher CAT levels were observed in the liver of Trematomus hansoni and Trematomus newnesi compared to Ttrematomus bernacchii. Yet, these levels were still lower than those typically in temperate organisms [55]. This finding is consistent with earlier studies showing lower CAT levels in red-blooded Antarctic fish compared to temperate species such as the Mediterranean gobiid Zosterisessor ophiocephalus [53]. These results suggest that Antarctic fish rely not on CAT for H_2O_2 scavenging, unlike Antarctic invertebrates, where high CAT activity is a crucial adaptation to high oxygen levels and •OH formation.

The anticipated coordination between SOD and CAT activities is not always observed, indicating that CAT does not solely scavenge H_2O_2 generated by SOD. Instead, other peroxidases, such as glutathione peroxidases, peroxiredoxins, and glutathione reductase, which converts oxidised glutathione (GSSH) to its reduced, active form (GSH), play crucial roles in H_2O_2 scavenging [53,55].

Studies on glutathione peroxidases are relatively recent, with the characterisation of the gpx-1 sequence in some Antarctic fish species occurring in 2015 [25]. Gene expression analyses in T. bernacchii have shown high variability in tissue gpx-1 mRNA accumulation, with the heart and liver exhibiting the highest transcription levels. This finding aligns with earlier studies [50,56,57] that measured high levels of active Se-GPx protein in the same organs of other Antarctic Nototheniidae species (Notothenia rossii, Dissostichus eleginoides, and T. newnesi). Similarly, GPxs have shown higher liver mRNA expression and activity levels than other tissues [25].

The study of peroxiredoxins in Antarctic fish presents a more complex and intriguing narrative. Prdx3, Prdx5, and Prdx6 characterisation in T. bernacchii was first documented between 2016 and 2019 [49,58]. It is common for fish, including Antarctic species, to have two isoforms of Prdx6 (6a and 6b). Research on peroxiredoxins in Antarctic fish consistently shows high activity levels of these enzymes in the liver. These pioneering studies highlighted several critical physiological characteristics of Antarctic fish antioxidant enzymes. Notably, the liver exhibits the highest enzyme activities, while muscle tissue shows the lowest, indicating a correlation between antioxidant enzyme levels and metabolic activity intensity.

Comparative analyses reveal that cold-adapted enzymes in Antarctic fish typically exhibit specific amino acid substitutions, increasing the number of polar residues like Arg, Glu, Ser, and Thr. These substitutions enhance the flexibility of the amino acid sequence, allowing the enzymes to function more effectively in the extreme cold conditions of the Antarctic environment [59–61].

3.1.2. Non-Enzymatic Antioxidant System

Vitamin E plays an essential role in non-enzymatic antioxidant defences. Due to its hydrophobic properties and consequent solubility in lipid membranes and lipoproteins, vitamin E is considered the most significant inhibitor of lipid peroxidation [62]. It scavenges lipoperoxide radicals involved in peroxidation chains [63], and its distribution in biological fluids and tissues strongly correlates with the amount of polyunsaturated fatty acids and oxygen exposure [64].

Gieseg et al. [65] compared plasma vitamin E levels in two Antarctic fish species (*Pagothenia borchgrevinki* and *T. bernacchii*) and two temperate water fish species (*Parapercis colias* and *Notolabrus fucicola*). The study found that Antarctic fish plasma had five to six times higher vitamin E concentrations than temperate fish species, indicating that Antarctic fish are subjected to more significant metabolic stress from free radical-mediated oxidation [65]. Colella et al. [51] confirmed this finding by detecting higher plasma vitamin E levels in all Antarctic fishes (*Notothenia coriiceps, Notothenia gibberifrons, Champspcephalus gunnari*) compared to *Oncochynchus mykiss*, with *N. coriiceps* showing levels approximately 12 times higher.

Ansaldo et al. [57] measured vitamin E levels in the liver, gills, heart and muscle homogenates of red-blooded (*Nototheniidae*) and white-blooded (*Channichthyidae*) Antarctic fish. They found no significant differences across families except in muscle, where higher vitamin E levels in Channichthyids correlated with a greater volume density of mitochondria [66].

The varying ability of Antarctic fish species to manage oxidative stress relates to their different lifestyles and metabolic rates. For instance, Klein et al. [67] noted that differences in the profiles of antioxidant defence systems adaptations among species are probably associated with their mobility levels. Specifically, the benthopelagic *N. rossii* exhibits higher spontaneous activity than the benthonic *N. coriiceps* and possesses greater antioxidant capacity observed in the brain and peripheral tissues (gills and white muscle). This capacity may involve non-enzymatic antioxidants like vitamins C and E.

Metal chelating molecules such as GSH and MT also play an important role in antioxidant defence. These molecules have a high percentage (around 30%) of cysteines, which have a scavenger action against ROS due to their thiol group [68,69]. While GSH is considered the primary defence mechanism [70,71], MTs are specifically induced in tissues in response to the risk of metal-induced oxidative stress [72].

The first metallothionein identified in Antarctic fish was purified and characterised in the icefish *Chionodraco hamatus* [73]. Subsequently, many studies were carried out to investigate the differential expression in different species [74,75] and in various organs of the same species [50], up to studying its molecular evolution in this peculiar taxonomic group [76,77].

The more active fish species *N. rossii* maintains increased GSH production in the gills and liver, evidenced by the increased activity of the enzyme activity of glutamate-cysteine ligase, to limit lipid and protein oxidative damage to levels comparable to those observed in the less active species *N. coriiceps*. However, GSH is utilised only in the liver of *N. rossii* for antioxidant purposes, whereas MT-like proteins are probably involved in the gills [67].

Another factor influencing the activation of non-enzymatic antioxidant defences in Antarctic fish is the natural occurrence of some metals (Cd and Cu) in coastal seawaters, reported to be about 70 ng/L for Cd and 150 ng/L for Cu [78].

Santovito et al. [50] conducted a study that established a link between metal presence and the levels of GSH and MTs in the tissues of two Antarctic teleosts: *T. bernacchii* and *T. newnesi*. The findings revealed that the liver accumulates the highest concentration of heavy metals, particularly in *T. bernacchii* with respect to *T. newnesi*, possibly due to their different feeding habits. *T. bernacchii* is a benthic species that primarily feeds on molluscs, polychaetes, and epibenthic crustaceans and is known to accumulate metals [79]. In contrast, *T. newnesi* predominantly consumes post-larval fish, krill amphipods and seaweeds, which accumulate lower amounts of cadmium [80]. Because of the high metal content, GSH and MTs accumulate significantly in both species' liver tissues [50].

A recent paper [7] explored the correlation between metal accumulation in the gills and liver of *T. hansoni* and the expression of MTs, assessed at both transcriptional and post-transcriptional levels. Following laboratory exposure to two treatments (1.57 μM Cu and 0.89 μM Cd), there was a notable increase in the concentrations of metals, particularly Cu, mainly accumulating in the liver tissue and Cd in gills. This metal accumulation corresponded with enhanced gene expression of MTs, specifically the MT-1 isoform, observed solely in the liver. Furthermore, the study also noted an increase in the active form of MT proteins, particularly in response to Cd, both in the liver and gills tissues. Despite evolving in extreme but very stable conditions, *T. hansoni* demonstrated significant phenotypic plasticity, indicating its capability to adapt to potential increases in environmental metal pollution.

3.1.3. Environmental Stressors

Despite its geographical isolation from other continents, Antarctic seawaters are increasingly threatened by anthropogenic pollutants transported primarily via oceanic currents and long-range atmospheric transport from industrialized regions [81]. To date, it is known, for example, that in addition to the well-known presence of high concentrations of heavy metals (of both natural and anthropic origin), traces of emerging contaminants like endocrine-disrupting chemicals, perfluorinated compounds, pharmaceuticals, and personal care products, have also been detected [82]. Another threat to this environment comes from the increasing effects of climate change.

Antarctic fish are particularly sensitive to these global changes as endemic species, which can induce elevated stress and prompt physiological responses. These responses are influenced by the extreme and stable conditions characteristic of the Antarctic environment [83]. The scientific community is actively investigating whether Antarctic fish possess sufficient physiological plasticity to adapt to these emerging challenges.

3.1.3.1. Thermal Stress

The different activations of antioxidant defenses could imply different abilities to deal with oxidative stress when facing environmental stressors, such as increasing seawater temperature.

As stenothermal species, thermal stress can potentially increase oxidative stress in Antarctic fish tissues, leading to imbalances in lipids, metabolites, immunological responses, and antioxidant defences. These complex antioxidant responses can vary depending on the degree of temperature increase, the duration of exposure, and the specific species or organs involved. Some Antarctic fish species are intolerant to sudden increases in temperature due to heat-induced hypoxia [84,85]. In other cases, studies have shown that a slight temperature increase can initially lead to a decrease in antioxidant defences, followed by a subsequent rise as the organism attempts to restore homeostasis [45,86].

An interesting case study concerns Prdxs. In *T. bernacchii*, some isoforms of these antioxidant enzymes are active at basal levels (5 and 6b), whereas others are induced only under thermal stress conditions (3 and 6a). Analyses of the protein structure have shown that the isoforms induced by increased temperature have similar characteristics to orthologous proteins in worm-temperature-adapted fish, stimulating phenotypic plasticity at the molecular level [49,58]. Further research is needed to determine whether these responses can counteract oxidative stress in warming seawaters.

3.1.3.2. Persistent Organic Pollutants (POPs)

Per- and poly-fluoroalkyl substances (PFAS) are emerging contaminants detected in remote locations far from their manufacturing sources, including Antarctica [87,88]. According to previous studies, variations in antioxidant enzyme activities indicate that PFAS exposure may disrupt the delicate balance of the antioxidant system. This disruption increases the production of ROS, affecting the mitochondria and initiating a cascade of events that amplifies cell apoptosis [89].

PFAS exposure induces the transcription of SOD and GPx genes in the liver and kidney of the Antarctic fish *T. newnesi* that show one more time to be the organs more active in the antioxidant response [90].

In a study by Regoli et al. [91], *T. bernacchii* was experimentally exposed to benzo[a]pyrene (a polycyclic aromatic hydrocarbon, PAH), 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), Cd and a combination of TCDD and Cd. The results suggest that high natural concentrations of Cd in Antarctic species (and metals in general) may restrict the ability of PAHs to undergo biotransformation, hence affecting their bioaccumulation inside the tissues and rendering Antarctic fish more vulnerable to these pollutants [92]. Organic compounds may also influence some metals' bioaccumulation by boosting their sequestration in the endoplasmic reticulum. GSH represented the first line of defence against Cd exposure (and combined with TCDD) in light of the increased total content in the exposed organisms' tissues. On the other hand, exposure to organic chemicals reduced the GSH content by inhibiting GR, which maintains the reduced, functionally active form.

Metals are known to react with SH-groups, thus altering the activity and structure of functional groups of proteins but also causing the oxidation of intracellular thiols, such as GSH and the onset of oxidative stress conditions [93]. In this respect, GSH has been shown to limit the inhibitory effects of trace metals on the biotransformation rate of aromatic xenobiotics [94].

The high natural concentrations of Cd in T. bernacchii were not paralleled by elevated basal levels of MTs. Induction of MTs showed a limited response, with only slight increases in fish coexposed to Cd and TCDD. Enhanced levels of GSH appeared to compensate for the limited response of MTs, confirming the importance of this thiol for Antarctic species with promptly available SH-groups for both antioxidant and metal-chelating functions [91].

3.2. Deep-Sea Fish

Deep-sea fish have evolved numerous adaptations to survive in the extreme conditions of the deep ocean [95]. Some of the most fascinating adaptations of deep-sea fish include bioluminescence, which allows them to produce light to attract prey or communicate with others in the dark depths [96]. Additionally, deep-sea fish have special adaptations to withstand the high pressure of the deep ocean, such as flexible and compressible bodies [96]. Their unique sensory adaptations, like large eyes and heightened sensitivity to vibrations, help them navigate and locate food without light [97]. These remarkable adaptations have enabled deep-sea fish to thrive in one of the most extreme environments on the planet [96]. The adaptations of deep-sea fish go even further, allowing them to survive and thrive in this harsh environment. One of the most remarkable adaptations is their ability to conserve energy, as food can be scarce in the deep ocean [98]. Many deep-sea fish have slow metabolic rates and specialised digestive systems that allow them to make the most of any food they find [99].

In addition to their physical adaptations, deep-sea fish have developed unique reproductive strategies to ensure survival. Some species have incredibly high fecundity, producing many offspring at once to offset the high mortality rate in their environment [100]. Others have evolved elaborate mating behaviours and communication methods to find partners in the vast expanse of the deep sea [101].

Furthermore, deep-sea fish have adapted to the limited oxygen availability in the deep ocean. Some species have specialised respiratory systems that allow them to extract oxygen from the water more efficiently, while others have developed unique haemoglobin structures to transport oxygen through their bodies [102].

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These diverse and complex adaptations have allowed deep-sea fish to carve out a niche in one of the most challenging environments on Earth, demonstrating the incredible ingenuity of evolution in the face of extreme conditions [103].

ROS are abundant in the upper layers of the oceans, but their concentrations decrease with increasing depth. In deeper regions, the exposure to oxidative stress is considerably lower because of reduced light irradiance, lower oxygen levels, and reduced metabolic activity [104]. When antioxidant defences of coastal and deep-sea species were compared, only the activity of GPx was observed to decrease with depth; CAT and SOD remained unchanged, which indicated that the dangers associated with ROS exposure did not appear to decrease in deep-sea areas, while other factors, like the presence of swim bladder, diet and pollutant exposure can significantly enhance the endogenous production of ROS in deep-sea fish species [104–106].

Similarly to coastal marine, pollution threatens species living in deep-sea areas, especially in locations with significant hydrodynamic activity like dense shelf water cascading, occurring every 6–10 years [105]. During this phenomenon, large amounts of organic matter and their associated non-polar contaminants are transported from the coastline to the deep sea, posing a significant danger to the deep-sea fauna [107]. It has long been known that deep-sea environments are affected by persistent organic pollutants, toxic metals, radioactive elements, pesticides, herbicides, and pharmaceuticals, with deep-sea sediments serving as a reservoir for contaminants [108]. Many research findings have demonstrated that deep-sea fish can accumulate significant levels of pollutants, sometimes even surpassing those found in coastal fish, while appearing to maintain their overall health status [109–112]. These studies point out the hypothesis that deep-sea fish species display efficient detoxifying mechanisms against environmental contaminant exposure, including antioxidant defences [113].

In their 2015 study, Ribalta and colleagues [113] picked out two crucial species for fisheries, *Solea solea* and *Dicentrarchus labrax*, within the coastal range (30–120 m). They selected the species *Trachyrhynchus scabrus* and *Mora moro* to represent the middle slope (900–1500 m) and identified *Alepocephalus rostratus* and *Cataetyx laticeps* as typical species found in the deep-sea slope (1500–3000 m) [114–116]. The interspecific variation of biotransformation enzymes was most likely influenced by diet, lifestyle, and phylogeny, as suggested by Ribalta et al. [113]. When considering habitat depth, the impact of these biological factors on detoxifying enzyme activities became more apparent, according to the findings of Ribalta et al. [113]. According to this relationship, *T. scabrus* and *M. moro* in the deep sea were potentially more tolerant and susceptible to organophosphate pesticide exposure, respectively [113]. In addition, in *A. rostratus*, low GPX activity was found in concomitance with higher CAT activity, which indicates that CAT activity in this species could be one efficient antioxidant mechanism for removing H_2O_2 [113]. This inverse relationship between antioxidant enzyme activities has been previously documented in fish and mammals [117–119]. It has been hypothesised that GPx is mainly used as a defense mechanism against metabolically produced ROS. In contrast, CAT could eliminate exogenously generated H_2O_2 in deep-sea fish [118]. Therefore, in deep-sea fish, CAT might have a more pronounced response than GPx following exposure to xenobiotics, which is in agreement with other studies [120].

Furthermore, investigating the regulation of CAT gene expression in deep-sea fish species can show how these organisms manage oxidative stress, a common challenge in the deep-sea environment [104]. Further food for thought comes from the observation that, in some cases, there is a differentiated response between males and females of the same species. For example, male specimens of *A. rostratus* living at a depth of 2000 m in the western Mediterranean Sea showed a significantly higher accumulation of CAT mRNA in the liver than specimens living in the Catalan slope (1500 m) [121].

Interestingly, liver levels of CAT activity are not similarly higher, indicating that the excess mRNA is not translated into activated protein. This absence of correlation between gene transcription and messenger translation is well documented in the literature referring to proteins of the antioxidant system of aquatic organisms [122,123], including fish [7,25,49,90], and many authors attribute it to a post-transcriptional control on protein synthesis. This regulation appears to depend on the development of stress granules, which are membrane-free cytoplasmic foci where messengers can be stored and translated later [124]. This characteristic seems to be associated with species that are exposed to stressful environments but do not undergo acute stress, which allows tissues such as the liver and muscle, which can undergo stress even in short periods, to react very quickly to acute stress when it occurs, in this specific case by producing more CAT in response to an abrupt increase in the rate of H_2O_2 generation.

Understanding the genetic mechanisms that govern the production of CAT, as the nucleation proteins of stress granules in non-model organisms [125,126], can provide valuable insights into the overall stress response of deep-sea fish. In addition to the scientific implications, research on CAT in deep-sea fish species has potential applications in biotechnology and medicine [127]. Insights gained from studying the unique properties of CAT in these organisms could inspire the development of novel antioxidant therapies or contribute to improving industrial enzymatic processes [127].

Though studies about deep-sea fish species are very few, for other deep-sea organisms, like sea-cucumber, it has been shown that MnSOD is essential for the survival of sea cucumbers in a dark, high-pressure, and low-temperature deep-sea environment [128]. Furthermore, Li et al. [128] research study indicated that MnSODs of deep-sea sea cucumber adapted to deep-sea environments through their amino acid changes in polarity, piezophilic behaviour, and local stability. In deep-sea fish species, SOD functional differences have been found between specimens belonging to the same species but living in different depths [119]. For example, specimens of *A. rostratus* living in the deep waters (1500 m) of the Blan-es canyon (northwestern Mediterranean Sea) showed significantly higher SOD activities in the liver than specimens living on the adjacent open slope (900 m) [119].

Other studies are needed to reveal the correlation between CAT, SOD and other antioxidant system components and extreme environments, which could help improve our understanding of the organism's adaptation mechanisms in the deep sea.

4. Conclusions and Perspectives

Although there is a great deal of data available to us on the antioxidant defenses of Antarctic and deep-sea fish, much still needs to be known in order to get a comprehensive picture. Fortunately, much of the research mentioned in this review is still in full development, and therefore it is expected that the understanding of this physiological system, so important for cell survival, will become even greater in the coming years.

It will be especially interesting to see how the combination of the two elements considered here (low temperatures and high depths) may together have contributed to the acquisition of an even more efficient antioxidant system. Examples include snailfish belonging to the genera *Careproctus* and *Paraliparis* [129]. These Antarctic fish live at depths between 200 and 2000 m and have been characterised mainly for the antifreeze properties of their blood and the characteristics of their sensory system [130,131]. However, they would be perfect model organisms to study the antioxidant physiological responses evolved in extreme environments.

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