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Innate immune and chronic heat stress responses in sturgeons: Advances and insights from studies on Russian sturgeons

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ABSTRACT

Chronic stress deteriorates the immune function of fish, thereby increasing their vulnerability to infections. However, the molecular and cellular mechanisms underlying stress-mediated immunosuppression and infection susceptibility in fish remain largely unknown. Understanding these mechanisms will contribute to improving fish welfare and their farm production. Herein, we review the challenges of sturgeon aquaculture in subtropical countries, where current climate change has giving rise to significant temperature increments during summer. This leads to the exposure of fish to stressful conditions during these months. Chronic heat stress deserves attention considering the rapid warming rate of the planet. It is already affecting wild fish populations, with disastrous consequences for sturgeons, which are one of the most endangered fish species in the world. In this context, we discuss the most recent advances through the studies on the effects of chronic heat stress on the innate immune components of sturgeons. To this end, we summarise the findings of studies focusing on the aquaculture of Russian sturgeons and observations made on other *Acipenser* species. Special attention is given to acute-phase proteins, as they might be valuable biomarkers of heat stress and infection, with applicability in monitoring the fish health status in farms.

Global warming challenges of sturgeon aquaculture in subtropical countries

Sturgeons are amongst the oldest non-teleost *Actinopterygii*. According to phylogenetic studies, they belong to the infraclass Chondrostei, order Acipenseriformes, and family Acipenseridae [1,2]. They are distributed in cold and temperate ecosystems all over the northern hemisphere, where they develop and reproduce generally at temperatures below 20 °C. Unfortunately, sturgeon wild populations have undergone irreparable losses, being one of the most endangered fish species in the world, with the recent extinction of some species and probable extinction of others in the coming years [3–6]. This is the consequence of anthropogenic activities, such as the construction of dams across rivers that obstruct spawning migrations and destroy natural breeding grounds and decades of overfishing for meat and caviar. This scenario has attracted attention to the *Acipenser* genus, increasing its ecological and economic relevance [7]. Moreover, it justifies a renewed interest in developing sturgeon aquaculture to restore sturgeon populations and supply the market with sturgeon products. In this context, the sturgeon aquaculture industry has experienced a significant increase worldwide in recent decades. This has boosted a parallel progress in sturgeon biology across multiple disciplines, such as evolutionary biology [8,9], genomics [10,11], and immunology [12–16], since all of them are indispensable for the growth of this sector [17]. Sturgeon immunology remains poorly understood, making its research challenging. It is also interesting from an evolutionary point of view, considering the ancient lineage of sturgeons. Amongst the *Acipenser* species, the Russian sturgeon (*Acipenser gueldenstaedtii*) is one of the most cultured worldwide. In Uruguay, it was successfully introduced in the '90 s, converting a country with no tradition of fish aquaculture into one of the top ten caviar producers worldwide, according to a 2017 global report [7]. Fish farming has an important socioeconomic impact as it promotes the development of isolated rural areas in Uruguay [18].

Sturgeon aquaculture is a promising venture; however, commercial-scale farming faces significant challenges because fish are exposed to several stressful factors during culturing. Since fish are poikilothermic, high water temperature is an important abiotic stress factor that influences larval development, body condition, and survival (reviewed in

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[19]). Moreover, effects of heat stress may intensify when it persists for long periods. The optimal water temperature for sturgeon aquaculture varies between 13 and 20 °C depending on the species and factors like age, size, and feeding rate [12,20–27]. Therefore, maintaining optimal water temperature is essential to avoid heat stress during sturgeon culture. However, maintaining this condition might become extremely difficult during the summer in countries with subtropical climates; this problem could worsen because the planet is warming faster than ever (https://news.un.org/en/story/2022/05/1117842). The severity of this problem is illustrated by an increase in the water temperatures of rivers in several countries, which are *Acipenser* habitats or hubs for *Acipenser* aquaculture, including Uruguay (www.ambiente.gub.uy/iSIA_OAN/), China, and France [12,28,29]. For instance, water temperature higher than 24 °C was reported in sturgeon farms in Uruguay, southern China, Russia, and Turkey [28–33]. In Uruguay, the exposure of Russian sturgeons to high temperatures (averaging 24 °C) overlaps with recurrent bacterial infections caused mainly by *Aeromonas hydrophila* [34], which is one of the most frequently detected bacteria in farmed Russian sturgeons [35,36]. In addition, white and green sturgeon larvae exposed to heat stress (26 °C) showed abnormal morphologies and/or higher mortality rates in comparison to control larvae cultured at 18 °C [24]. The detrimental effects of heat stress on sturgeon health represent an economic problem for farms, challenging the development and sustainability of sturgeon aquaculture [37]. Concerns about the impact of global warming on sturgeon aquaculture are increasing, and recent studies have examined the effects of warm and extremely high temperatures (nearly 30 °C) on several organs and physiological functions of different *Acipenser* species [26,31,32,38–42]. Notably, temperature training (several rounds of fluctuations from 20 to 24 °C) reduced gene dysregulation subsequent to a heat shock in Atlantic sturgeons, suggesting that temperature training could improve the heat resistance of sturgeons during farming [39].

Chronic heat stress weakens sturgeons' innate serum components, involving a metabolic reprogramming of the liver

It has been well established that water temperature influences teleost fish physiology, including the immune response [43–45]. In sturgeons, the effects of temperature on fish physiology have been poorly examined in the last century, probably because public data on the genome or transcriptome of several organs (including the liver and immune-related organs) of *Acipenser* species were unavailable until 2010 [46]. Earlier studies have described the development of a cortisol response simultaneous to an increase in anaerobic metabolism (measured in terms of lactate increment) in green and white sturgeons exposed to acute temperature increments or during the summer [47,48]. However, the

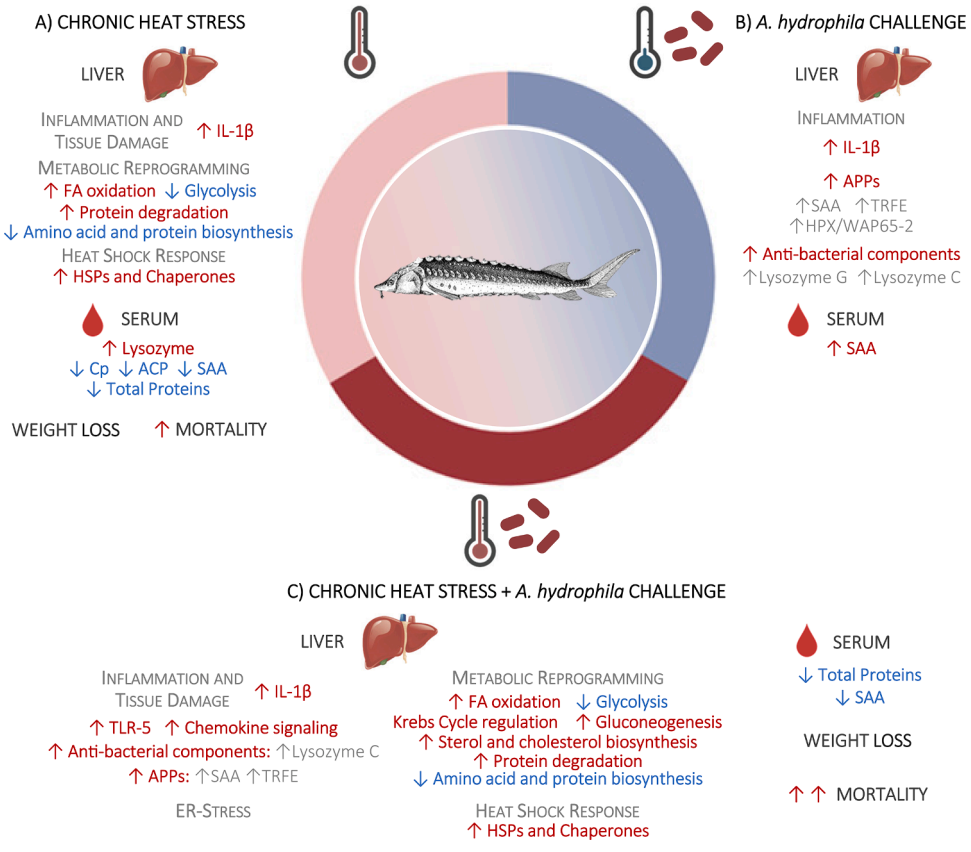

Fig. 1. Summary of the main alterations found in Russian sturgeons exposed to chronic heat stress and/or challenged with ***A. hydrophila***. (A) Chronic heat stress-induced a liver inflammatory response and upregulated genes related to heat-shock response and lipid and protein metabolism, to meet energy demands in Russian sturgeons. This metabolic reprogramming reduced liver protein synthesis [41], which might explain the decrease in Cp (ceruloplasmin), ACP (alternative complement pathway), SAA (serum amyloid A), and total proteins observed in the serum of heat-stressed sturgeons [12,41]. (B) The challenge with *A. hydrophila* in Russian sturgeons maintained at tolerable temperatures induced an anti-bacterial response characterised by the liver expression of IL-1β and lysozymes G and C and induction of acute-phase proteins (APPs), namely HPX/WAP65-2 (hemopexin), TRFE (serotransferrin), and SAA [41,77]. Moreover, the liver expression of SAA correlated with the increase in their serum levels, indicating that SAA behaves as a positive APP in Russian sturgeon [77,123]. (C) Chronic heat-stressed Russian sturgeons challenged with *A. hydrophila* mounted a metabolic reprogramming similar to fish exposed to chronic heat stress and presented an altered anti-bacterial response. Although several immune-related genes were up-regulated in the liver, the diminished liver protein synthesis led to a significant reduction of serum total proteins, including SAA. Furthermore, the persistence of heat stress resulted in signs of endoplasmic-reticulum (ER) stress, weight loss, and increased mortality, with the latter being higher after bacterial challenge [41].

magnitude of this cortisol response may vary amongst *Acipenser* species, according to a recent comparative study conducted in evolutionarily distant Atlantic and shortnose sturgeons [49]. The effect of chronic heat stress on sturgeon innate immunity was first reported in a study in 2017 investigating the extent of influence of summertime temperatures (averaging 24 °C) on some innate components of farmed Russian sturgeons [12]. That study was focused on the alternative complement pathway (ACP), lysozyme, and ceruloplasmin (Cp), since innate immunity plays an important role in fish defence, and simple activity assays based on non-species-specific reagents could be applied for their determination. Interestingly, long-term exposure to stressful warm temperatures caused significant alterations in these components, including a decrease in ACP and Cp serum levels, and a moderate lysozyme increase, compared to their levels in winter (13 ± 2 °C). Furthermore, the role of temperature in these deleterious effects was confirmed, since similar alterations in ACP, Cp and lysozyme were observed in Russian sturgeons exposed to heat stress for several weeks under laboratory-controlled conditions (Fig. 1A) [12]. A similar reduction in complement levels has been observed in some teleosts under chronic stress [50,51]. The decrease in ACP and Cp levels may be attributed to changes in protein synthesis and/or catabolism in the liver, where they are mostly produced. This hypothesis is consistent with the parallel reduction in total serum protein levels [12], which is a sign of chronic stress and has been described in other teleosts under long-term stressful conditions [52,53]. The mechanisms underlying the decrease in serum protein levels of fish under chronic stress have not been completely elucidated; however, in the case of Russian sturgeons, a tight liver metabolic reprogramming may be involved. The analysis of the liver transcriptome of Russian sturgeons under chronic heat stress, showed that they mount several energy-costing adaptive responses sustained by the mobilisation of almost all energy sources [41]. Significant transcriptional changes were observed, including the upregulation of genes encoding some proteolytic enzymes (elastase-3B and cathepsins) and downregulation of genes involved in amino acid biosynthesis and protein translation machinery (including 40S and 60S ribosomal components and translation initiation factors) [41]. Similar regulatory effects interfering with mRNA-directed protein synthesis have been described in the larvae of other *Acipenser* species under prolonged heat stress [24,42]. The observed scenario is expected, since the impact of increased temperatures on liver protein synthesis in teleosts has already been demonstrated [54,55]. Moreover, acute heat stress has been reported to increase the levels of free amino acids and upregulate genes related to ubiquitin-dependent proteolysis in the livers of Yangtze sturgeon (*A. dabryanus*), providing evidence that heat stress induces liver protein degradation in sturgeons [32]. Similarly, the downregulation of processes that affect protein biosynthesis (rRNA processing, ribosome biogenesis, and RNA polymerase activity) has been described in the muscles of Atlantic sturgeons exposed to acute heat stress [49]. The protein biosynthesis arrest and promotion of protein degradation observed in the livers of chronically stressed Russian sturgeons could explain the reduction in ACP and Cp activities, although their corresponding genes were not downregulated. As an exemption amongst complement components, clusterin, a chaperone known to be induced during heat shock responses, was found to be upregulated in the liver of Russian sturgeons exposed to chronic heat stress [41]; this upregulation, together with that observed for other chaperones and heat shock proteins (HSP) in sturgeons [38,39], likely maintains and restores the folding of stress-denatured proteins, preventing their aggregation and degradation. However, the contribution of clusterin to the reduction in serum ACP activity needs to be examined because it acts as a regulator of the terminal complement pathway in mammals [56]. Additionally, lysozymes, involved in innate defence, seem to be upregulated by stress-induced hormones, indicated by increased serum lysozyme activity in sturgeons under acute [57] and chronic heat stress [41]. The transcriptional upregulation of lysozyme C in the liver was observed in chronically stressed Russian sturgeons (Fig. 1A) [41]. Furthermore, it is probable that other cell types may contribute to serum lysozyme activity because teleost leukocytes and gill epithelial cells can synthesise and secrete lysozymes into the bloodstream [58]. The increased lysozyme levels in circulation likely acts as a protective barrier against multiple opportunistic bacteria, which could reach the bloodstream because of the damage caused by heat stress on the integrity of physical barriers. Long-term exposure to increased temperatures has led to severe alterations in the physiological functions of the intestine in juvenile sturgeons, including marked signs of necrosis in mucosal epithelial cells and the disruption of the balance of intestinal microbiota, facilitating the growth of pathogenic bacteria [40]. Moreover, damage to the intestinal barrier caused by heat stress likely allows bacterial components such as endotoxins to enter the mucosa, triggering the release of pro-inflammatory components, as suggested in other animals [59]. Histopathological changes in other organs, including the gills [31] and liver, have also been described in sturgeons subjected to stressful warm temperatures for long [41] and short periods [32]. As previously mentioned, analysis of the liver transcriptome revealed that chronic heat stress triggers adaptive responses involving several energy-consuming processes in Russian sturgeons, and the induced complex metabolic reprogramming generates high levels of undesirable products (lipids, reactive oxygen species, and reactive aldehyde derivatives) that contribute to cell damage and inflammation. Accordingly, the accumulation of cytoplasmic lipid vacuoles and necrotic foci in the liver was observed in parallel with IL-1β upregulation and inflammatory cell infiltration (Fig. 1A) [41]. These observations reveal that innate immune cells are indeed active during heat stress; however, when the stressful conditions persist, the sustained generation of cell-damage-derived components trigger an inflammatory reaction that amplifies tissue damage, rather than tissue repair. Overall, the chronic heat stress response in sturgeons compromises its innate defences because the metabolic reprogramming induced to maintain homoeostasis diminishes protein biosynthesis and accelerates proteolysis in the liver, where several proteins linked to innate defences are produced. This generates danger signals that trigger a sustained activation of innate cells, resulting in a harmful inflammatory reaction likely followed by cell exhaustion.

Acute-phase proteins (APPs) as tools for monitoring sturgeon health in farms

Monitoring health status of fish during their culture could help tackle sturgeon aquaculture challenges by preventing infection outbreaks and controlling the spread of diseases. However, the molecular tools required for this monitoring are not commercially available. Immunoassays are highly sensitive and specific, amenable to an assay format which would be favourable for use in farms, such as the immunochromatographic lateral flow assay [60]. Therefore, serum biomarkers that reveal early altered health conditions should be identified. Amongst other plasma proteins, APPs are ideal candidates for measurement in serum samples because they are highly regulated by inflammatory cytokines (i.e. IL-6, IL-1β, and TNF-α, which are induced a few hours after an innate recognition) and predominantly synthesised by the liver and secreted into the bloodstream [61–63]. In mammals, more than 200 biochemically and functionally diverse APPs are present. Their levels usually increase or decline within 72 h post-infection [64,65], and they can remain altered by persistent danger signals [66,67]. Depending on their increase or decrease in serum concentrations, APPs are respectively distinguished as positive and negative. Major APPs are induced over 100–1000-fold and considered excellent biomarkers of infection and/or inflammatory disorders in humans and veterinary animals [62,63,68]. Several APP orthologues have been identified in teleosts, and their gene expression and serum levels are quantified in infection models [69–74]. Interestingly, teleost APPs have a different number of gene isoforms from their mammalian counterparts; they are extrahepatic and expressed particularly in other immune-relevant organs [69,75,76].

As previously mentioned, data on sturgeon innate defences

(including the characterisation of the acute phase response [APR]) were scarce until the advent of modern molecular biology tools that made genomic and transcriptomic studies possible. Sturgeon APPs were initially investigated using the Russian sturgeon as a model. A biased approach was adopted, guided by the knowledge of proteins that act as APPs in vertebrates, particularly teleosts [77]. Thus, hemopexin (HPX/WAP65–2), serotransferrin (TRFE), and serum amyloid A (SAA) were identified as potential positive APPs, based on their transcriptional upregulation in the livers of Russian sturgeons cultured at tolerable temperatures and challenged with live *Aeromonas hydrophila* (Fig. 1B) [77], one of the major bacteria detected in sturgeon farms worldwide [13,34,35,78]. HPX/WAP65–2 belongs to the fish hemopexin family and its mammalian orthologues are hemopexins with hemoscavenging activity. In Russian sturgeons, hepatic *hpx/wap65-2* upregulation was lower than that in various teleosts during bacterial infection [79,80]. TRFE could be more sensitive than HPX/WAP65-2 according to the results obtained in Russian sturgeons [77], and its early hepatic upregulation could be sustained for a few weeks, according to its increased levels in the liver of *A. schrenckii* infected with *Mycobacterium marinum* [67] and serum of *A. trasmontanus* challenged with the fungus *Veronaea botryosa* [81]. The sturgeon TRFE response seems to be similar to that found in some teleosts challenged with bacteria (including *A. hydrophila* [82–87]), although it has been described as a negative APP in other teleosts [70,88,89]. Nevertheless, differences in the observed TRFE responses between fish might be due to distinct stimulation conditions, including dose, via, and the type of stimulus involved. Compared to HPX/WAP65-2 and TRFE, SAA serves as a more robust positive APP in Russian sturgeons because *saa* hepatic upregulation was consistently more intense [77]. One *saa* gene was found in *A. ruthenus* genome (XM_034904786.2), which is similar to that in zebrafish and Atlantic salmon (*EnsemblGRCz11, Salmobase*). The involvement of SAA in the APR in sturgeon agrees with its role as APP in several teleosts, including salmonids, zebrafish, carp, and orange-spotted grouper [90–92]. The correlation between the hepatic expression and serum levels has not been examined for most APPs identified in sturgeons. However, in the case of SAA, serum SAA concentrations increased significantly and correlated with liver *saa* mRNA levels in Russian sturgeons challenged with *A. hydrophila* (Fig. 1B) [77]. However, the *saa* hepatic upregulation in Russian sturgeons had slower kinetics than that in mammals. It was detected after only 72 h post-challenge under the assayed conditions, although it could be sustained for several weeks [67]. The slower response observed in sturgeons compared to mammals may be related to the differences in the thermal physiology between these species. Mammals are endothermic organisms, who have more energy (by an order of magnitude) available for physiological functions than a typical ectotherm of similar mass [93]. Moreover, in a murine model of *Salmonella typhimurium* infection, *saa*-deficient mice showed a higher bacterial load in the liver and spleen than their wild-type counterparts, indicating the relevance of SAA upregulation during APR [94]. However, the current understanding of cellular and molecular mechanisms underlying the protective effects of SAA is limited. In vitro studies have suggested that SAA can bind to gram-negative bacteria, acting as an opsonin that potentiates phagocytosis [95,96]. This binding ability appears to be shared by SAA in a wide range of species, including fish [76,95,96]. In any case, the acute SAA response seems to be an infection trait in organisms ranging from chondrosteans to mammals, contributing to their natural defence against bacterial infections.

In addition to HPX/WAP65–2, TRFE, and SAA, hepcidin, haptoglobin, intelectin, and the pentraxin CRP/SAP were identified and evaluated as putative APP candidates in sturgeons. Teleosts have two functionally different hepcidin genes, one involved in iron metabolism (*hamp1*) and the other in antimicrobial effects (*hamp2)*. Contrastingly, in sturgeons, these two functions appear to be represented in a single gene (*hamp*) [97]. The hepatic regulation of *hamp* expression during infection with gram-negative bacteria showed contrasting results amongst *Acipenser* species. It was not upregulated at the transcriptional level after intraperitoneal bacterial challenge in *A. baeri* [97] or *A. gueldenstaedtii* [77], but exhibited an increase in bacterial-challenged *A. dabryanus* [98]. Dissimilar results may have occurred due to differences in the route of infection and/or the pathogenicity of the bacterial strains used. Although further experiments are needed to determine whether HAMP is a positive APP, it does not appear to be a robust APP in *Acipenser*. Haptoglobin (HP) is a plasma protein that binds to cell-free haemoglobin and inhibits its oxidative activity [99]. One *hp* gene was found in the *A. ruthenus* genome (XM_058994093.1), and one *hp* sequence was identified using transcriptomic data from *A. oxyrinchus* [81]. Although HP has been proposed as a positive APP [100,101], its serum levels in *A. transmontanus* were found to diminish several weeks post-challenge with *V. botryosa* [81]. Regarding intelectin (ITLN), they belong to a family of X-type lectins that comprises various conserved isoforms in vertebrates, although their expression patterns and functions differ considerably amongst and within species [102]. Expression of various *itln* isoforms was reported in teleost fish, and some of them were upregulated in the liver after a bacterial challenge [103–107]. In *A. gueldenstaedtii*, only one liver *itln* isoform has been identified [77], which has high similarity to two intelectin-like sequences of *A. ruthenus* [10] and more similarity to *itln*-2 of *Danio rerio* [103]. RT-qPCR and RNA-Seq analyses showed that *itln* was not upregulated in *A. gueldenstaedtii* liver upon *A. hydrophila* challenge, suggesting that it does not behave as a positive APP, at least under the conditions analysed [41,77]. Pentraxins are a superfamily of multimeric proteins that are highly evolutionarily conserved and act as soluble receptors of the innate immune system [108]. Amongst mammalian pentraxins, C-reactive protein (CRP) and serum Amyloid P (SAP) stand out for their role in the APR, but their role as clinical indicators of inflammation varies amongst mammals [109,110]. In teleosts, multiple copies of *crp* and *sap*-like genes have been identified, and phylogenetic studies have indicated that their protein products constitute a single clade, usually known as *crp/sap* [111–114]. The ligand-binding properties of fish CRP/SAPs seem species-specific, with some members exhibiting greater similarity to CRP and others to SAP [113]. In fish, the CRP/SAP involvement in the APR is limited to a few teleost species, in which a null or slight effect on CRP/SAP serum levels was observed after stimulation with microbial components or bacterial challenge [75,115-122]. Sturgeon CRP/SAP pentraxins have been identified and found to be almost identical within the *Acipenser* genus (> 95 % identity) and conserved across distant ray-finned fish from sturgeons to teleosts (50 % identity) [123]. Furthermore, the identified *Acipenser* CRP/SAP pentraxins belong to the universal CRP/SAP subfamily, which comprises genes from mammals to fish and is grouped separate from the CRP/SAP subfamily specific to fish and amphibians [123,124]. Russian sturgeon CRP/SAP was found to be constitutively expressed but not modulated by an *A. hydrophila* challenge [123], suggesting that it does not act as an APP. This agrees with the observations made in some teleosts [87,124,125]. However, sturgeon CRP/SAP might be upregulated or even downregulated by other pathogens, as illustrated in Atlantic salmon infected with *A. salmonicida* [75]. In mammals, CRP and/or SAP pentraxins are rapidly and highly induced at trace levels. Contrastingly, in Russian sturgeons and some teleosts, CRP/SAP would be constitutively present in the circulation and poorly regulated or unchanged during bacteria-induced APR, suggesting that its most important function might not be related to its APP behaviour.

As can be seen from the studies discussed above, most knowledge about APR in sturgeons comes from bacteria-challenged models. However, viral diseases can also affect farmed sturgeons because many viral agents have been reported in different sturgeon species [126]. However, reports of APR using viral models are scarce. Transcriptomic analysis of the Bester sturgeon (*Huso huso* × *A. ruthenus*) injected with a synthetic analogue of viral double-stranded RNA (poly I:C) showed that *trfe* and *hpx/wap65* were amongst the most expressed genes in the liver transcriptome; however, hepatic differentially expressed genes in response to poly I:C have not been reported [127].

Finally, considering their potential as biomarkers of inflammation, APPs could also be regulated during the chronic heat stress response due to the development of liver inflammation. Russian sturgeons exposed to high stress conditions (a temperature gradient from 24 to 30 °C over 20 days) exhibited a decrease in SAA serum levels, which occurred parallel to a decrease in ACP activity and an increase in lysozyme activity (Fig. 1A). The latter two changes reproduced the alterations observed in sturgeons reared during the summer season in Uruguay [123]. Additionally, in an unbiased analysis of hepatic transcriptional changes elicited by chronic heat stress (exposure to 30 ± 1 °C for five weeks), down-regulation of SAA expression did not occur [41]. This suggested that the global alteration of hepatic protein metabolism is responsible for the observed decrease in serum SAA levels. Furthermore, no changes in serum CRP/SAP levels [123] or hepatic *hpx/wap65-2* or *trfe* expression [41] were induced by chronic heat stress, and most of the upregulated genes were associated with the conventional cellular response to stress, including HSPs, chaperones, several proteolytic enzymes, and enzymes related to omega-fatty acid degradation. The cytokine IL-1β was the only inflammatory component upregulated in the liver of chronically stressed surgeons [41]. This is consistent with the biological processes upregulated by heat stress in the liver and epithelial cell lines of the Atlantic sturgeon [38,39]. Considering the tight reprogramming of liver metabolism during chronic heat stress, inflammatory and chronic stress biomarkers can be identified by evaluating both hepatic expression and serum levels. Alternatively, post-translational modifications may occur in APPs due to thermal stress [128], opening the possibility of using them for detecting fish stress responses.

Detrimental effects of chronic heat stress on the sturgeon anti-bacterial response

Cross-susceptibility refers to how the exposure to a first stressor causes the organism to be more susceptible to a second stressor. This situation is described during fish exposure to abiotic stressors, such as temperature and salinity (reviewed by [129]). As contact with micro-organisms also denotes a challenge, a cross-susceptibility is suspected in the increased predisposition to infection exhibited by fish reared at non-tolerable temperatures. Multiple mechanisms are likely responsible for this increased vulnerability to pathogens, including a general immunosuppression status [130–132]. In sturgeons, the observed metabolic reprogramming and weakening of innate defences caused by chronic heat stress probably contributes to this immunosuppression. The most recent advances in the characterisation of immune responses in heat-stressed vs. non-stressed sturgeons came from transcriptomic studies of fish livers and whole bodies [41,42]. As already mentioned, the bacterial challenge of Russian sturgeons maintained at a tolerable temperature induced hepatic upregulation of genes encoding APR-related proteins, including TRFE and SAA [67,77]; the latter, in some studies, was also found to increase in the serum [77,123]. Additionally, the hepatic upregulation of inflammatory cytokine IL-1β and the C- and G-type lysozymes were induced by *A. hydrophila* challenge (Fig. 1B) [41]. However, when Russian sturgeons were exposed to chronic heat stress many of these immune mechanisms elicited by this challenge were compromised. Thus, chronic heat stress caused liver inflammation and tissue damage, which are probably linked to the metabolic reprogramming needed to maintain homoeostasis. Although heat-stressed sturgeons showed hepatic expression of immune-related genes, it was not significantly increased by *A. hydrophila* challenge. Moreover, this hepatic response (characterised by upregulation of HSPs, chaperones, and IL-1β) seemed to condition putative changes elicited by bacteria challenge, rather than enhancing anti-bacterial defences. Furthermore, the bacteria-induced increase in serum SAA levels was abolished under chronic heat stress, resulting from the reprogramming of liver protein metabolism that favoured proteolysis and interfered with protein biosynthesis (Fig. 1C) [41]. Similar dampening of the innate immune response was observed in developing lake sturgeons exposed to warm temperatures [42]. In this study, transcriptomic analysis of the sturgeon whole body demonstrated that long-term exposure to heat stress induced an adaptation response that upregulated the genes involved in pathogen recognition (MyD88 and NF-ƘB), effector mechanisms (C3 and lysozyme C), and lipid metabolism (CPT1). However, this response conditioned the fish response to lipopolysaccharide (LPS), resulting in a diminished upregulation of several genes involved in innate immunity (MyD88, TICAM-1, C3, IL-1β, IL8, TNFα, and lysozyme-C), lipid metabolism (PLA2 and CPT1), and heat-shock responses (HSP70). Moreover, the LPS-induced immune response was sustained for seven days, exhibiting higher levels in the control than in the heat-stressed sturgeons. This revealed that chronic heat stress could influence long-term immune responses. Developing sturgeons under thermal stress exhibited a lower metabolic capacity; thus, they would not have endured the energy cost demanded by warmer temperatures, compromising the induction of innate immune responses [42]. Finally, the effect of a persistent heat-stressing condition on the antifungal immune response of white sturgeons was examined [27,133]. An increase of 5 °C from the temperature experienced in nature represented a high risk of severe fungi dissemination and mortality. Moreover, heat-stressed white sturgeons infected with *V. botryosa* developed an enhanced inflammatory response during the chronic phase of the infection compared to that of the controls, including moderate APP expression and the upregulation of cathelicidin and inflammatory cytokines in the spleen; however, this response failed to prevent the spread of the pathogen, which is associated with disease progression, and higher mortality [27,133].

Conclusion and perspectives

Owing to the current scenario of global warming, farmed sturgeons are exposed to long-term heat stress, threatening fish health and aquaculture sustainability. Unfortunately, global warming is increasing, justifying an urgent focus on this matter. Studies on various *Acipenser* species have demonstrated that chronic heat stress weakens innate defences, likely increasing their vulnerability to infection. Mechanisms involved in the weakening of this defence include the reduction in innate immune signalling and plasma components associated with rapid effector responses against pathogens (complement system and APPs).

The effects of chronic heat stress during sturgeon aquaculture could be counteracted by developing practical tools for the rapid detection of infection and acute and persistent stress conditions. Advances made in this direction have shed light on the involvement of some innate components in sturgeon APR. SAA and TRFE might be useful as serum biomarkers of infection in fish culturing at non-stressing temperatures, although they should be tested under a variety of inflammatory and stress conditions. The early detection of infection may aid in preventing pathogen spread in farms. However, transcriptional changes observed in different tissues of stressed sturgeons may be correlated at the serum level, which could help identify plasma chronic stress biomarkers. APPs or any putative serum protein identified as an inflammatory or chronic stress biomarker requires the development of practical assays and their evaluation throughout the year in farmed fish to be validated for their applicability in monitoring sturgeon health status. Furthermore, this validation should be carried out for each *Acipenser* species, given that the family Acipenseridae spans species that arose millions of years apart, with variable life histories, broad geographical distribution, and distinct responses to stress [49]. Stimulation treatments aimed at enhancing sturgeon defence and/or antioxidative mechanisms have been performed using a variety of products, including yeast cell-wall extracts [12], β-glucans [81,134], recombinant IL-1β [135], and natural plant derivatives [136]. However, the responses elicited by these treatments remain poorly understood and likely depend on many factors (such as dose, route of administration, and time of treatment). Therefore, an in-depth understanding of the responses triggered by immunostimulants is required to evaluate their effectiveness against a particular pathogen.

Factors such as the pathogen type (viruses, bacteria, fungi, protozoa, and worms) and localisation (mucosal vs. non-mucosal tissues) determine the type of immunostimulation needed for an effective and beneficial response. Contrasting results were found when β-glucan stimulation was used to improve the defence against bacteria (*Flavobacterium columnare* [134]) and fungi (*V. bodryosa* [81]). Although the tools for studying sturgeon immunity are still limited, this is an emerging and promising area of research. Considering the relevance of innate immunity in fish defence and innate cell plasticity in detecting a wide range of danger signals, we could aim for a long-term functional reprogramming that will result in enhanced responsiveness to subsequent triggers.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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