Stress and Immunity in Fish

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Lluis Tort and Joan Carles Balasch

Abstract

Fish inhabit microbial- and parasite-enriched environments that constrict the adaptive choices and evolutionary pathways of regulatory physiological systems. Teleost immune architecture reflects those selective pressures, and the modulation of immune performance by glucocorticoids and other mediators of perceived stress have sculpted the type, intensity and scope of stress-related immunity in fish. In this chapter, the immune response to stress in teleosts and the role of the principal mediators such as hormones, cytokines and neurotransmitters are reviewed. The interactions between the immune, endocrine and neural regulatory systems and the influence of the local environment in the response are also considered.

Keywords

Stress · Innate immunity · Adaptive immunity · Teleosts · Neuro-immune axis · Environmental stressors

L. Tort (✉) · J. C. Balasch
Department of Cell Biology, Physiology and Immunology, Universitat Autonoma de Barcelona, Barcelona, Spain
e-mail: lluis.tort@uab.es; JoanCarles.Balasch@uab.cat

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Abbreviations

Ag	antigen
AID	activation-induced deaminase enzyme
AMP	antimicrobial protein
APC	antigen-presenting cells
APP	acute-phase protein
APR	acute-phase response
BMR	basal metabolic rate
CSR	class switch recombination
DAMPs	danger/damage-associated molecular patterns
E2	17β-oestradiol
EE2	ethinyloestradiol
FDC	follicular dendritic cell
GR	glucocorticoid receptor
HIRECs	human-induced rapid environmental changes
HPG	hypothalamic–pituitary–gonadal axis
HPI	hypothalamic–pituitary–interrenal axis
HPT	hypothalamic–pituitary–thyroid axis
IFN	interferon
IGF	growth hormone (GH)/insulin-like growth factor axis
LLPC	long-lived plasma cell
LPS	bacterial lipopolysaccharide
MHC	major histocompatibility complex
MMC	melanomacrophage centre
MR	mineralocorticoid receptor
NK	natural killer cells
PAMP	pathogen-associated molecular pattern
PKD	proliferative kidney disease
PRR	pattern recognition receptor
RAG	recombination-activating gene
ROS	reactive oxygen species
SC	sympatho-chromaffin axis
SHM	somatic hypermutation
TCR	T-cell receptor
TLR	Toll-like receptor
VLRs	variable lymphocyte receptors

20.1 Introduction

Environmental changes, unpredictable or expected, persistent or serendipitous, biotic or abiotic, mellifluous or obnoxious, constitute the fuel upon which selective processes boost normal or abnormal stress responses (Romero et al. 2009). A majority of these changes may elicit harmless adjustments in the physiological constraints that define the tolerance limits of core temperature, osmolyte levels or acid–base balances. Others, unexpected, rare and intense changes may force stressful, allostatic adjustments, enhancing the activation of neuroendocrinological and immune cascades, in an effort to reverse unsafe levels of endogenous variables. In addition, a minority of those variations, mainly induced by human-related industrial and productive activities, may severely compromise the health of organisms in a species-specific manner, mostly in local scenarios in which the defining parameters of niche minutiae may change abruptly (Halpern et al. 2008). A classic example is the impact in coastal fish of endocrine disruptors, whose concentration may change dramatically due to aquaculture or industrial run-offs, fluvial outflows and seasonal weather episodes, in the reproductive, tiroidal and stress neurohormonal cascades (Gaw et al. 2014; Szwejser et al. 2017). Confronted with such human-induced rapid environmental changes (HIRECs), stressed individuals skew their energetic budgets, dedicated to metabolism, reproduction and growth, in favour of physiological trade-offs, usually weighted by the species-specific scope and versatility of the evolved adaptive behavioural repertories that allow for coping with environmental stressors, but also by the efficiency and unfolding capabilities of the immune response (Balasch and Tort 2019). Accordingly, the stress response becomes a result of interactive processes between nervous, immune and endocrine systems, devoted to overcome the challenge caused by the stressor and to compensate for its effects, a connection already observed some decades ago when several works demonstrated that not only hormones altered immune functions but also that the immune mediators influenced the neuroendocrine system (Chiappelli et al. 1993). As we discuss below, both stress-related and immune physiological systems share common components and pathways, but a precise description of neuroimmunoendocrine crosstalk is still lacking for fish species. In this sense, the molecular, cellular and systemic scaffolding of stress and immune responses may be considered a common mechanism of defences that share the burden of limited metabolic budgets in what can be described as a collaborative network of mutual influences.

Any particular stressor (or combinations of stressors) may generate an evolutionarily conserved *adaptive* stress response or, alternatively, maladaptive ones if the intensity, persistence and resilience values of the stressor depart from the "classical" selective pressures, such as depredation, parasitism, or intraspecific and interspecific competition for resources and sex partners, in a given ecological niche. Considering fish species, the evolutionary road to immune sense—i.e. the meaningful detection of self- and non-self-antigens—and sensitivity—measured as the minimum defensive response threshold to foreign microorganisms or xenobiotics—is paved with hardwired anticipatory stress

responses constructed during the convoluted evolutionary history of survival and extinction in microbial-rich environments.

20.2   The Aquatic Constraints on Fish Immunity: Navigating Stressful Seas

Fish inhabit aquatic environments prone to pathogen spillover and xenobiotic spreading that stress their immune systems, usually less complex, in terms of both diversity of cellular phenotypes and specificity of antigen recognition components, than those of mammals (Flajnik 2018). Ocean microbiota abundances range from estimates of 10^4 to 10^6 cells mL^{-1}, or, in the case of virus (dominated by phages), up to 10^8 viruses mL^{-1} in open waters and 10^{31} in the sub-seafloor (Whitman et al. 1998; Middelboe and Brussaard 2017; Cai et al. 2019). In open oceans, the taxonomic and functional composition, distribution and stratification of microbial communities correlate strongly with temperature and dissolved oxygen (Brum et al. 2015; Sunagawa et al. 2015), with salinity, nutrient content and currents seemingly playing minor roles. Microbial communities in aquatic dwellings are characterized by (1) differential local and global clustering of viral and bacterial communities, influenced by host–pathogen interactions, hydrogeographic features or biogeographical regimes (Brum et al. 2015), (2) complex interactions between bacteria and virus (Breitbart 2011; Orsi 2018) that influence biogeochemical cycling, bacterial gene expression (due to horizontal gene transfer) and pathogenicity (extensive to marine invertebrates and vertebrates), (3) high persistence (thousands of years) of viral and bacterial communities in the energy-starved seafloor (Lomstein et al. 2012; Cai et al. 2019) and (4) huge genetic diversity reservoirs, especially in deep-sea sediments crowded by viral phenotypes, which may fuel evolutionary changes (Jousset et al. 2017). Virus and transposable elements have been postulated as the origin of early immune pathways in marine basal vertebrates (Broecker and Moelling 2019), and fish house large numbers of viruses, prone to jump between hosts (Shi et al. 2018; Geoghegan et al. 2018). In fact, the microorganism richness of aquatic realms continues to impact the co-evolution of complex host–pathogen interactions (Zhang et al. 2018), and maybe even influenced the faster rate of genetic evolution in teleost fish compared to mammals (Takezaki 2018). This, in turn, may have facilitated their bewildering morphological and physiological diversity. Fish show extremely diverse lifestyles, having colonized abyssal wastelands (Swann et al. 2020), submerged murky caves (Maldonado et al. 2020), polar waters (Farrell and Franklin 2016), hypoxic sulphidic mangroves (Rossi et al. 2019) and desiccated ponds (Wright and Turko 2016) due to their remarkable phenotypic plasticity. Coupling the expression of fish genomes to changing environmental constraints allows for the expression of plastic phenotypes, but the vast majority of studies of developmental or behavioural plasticity in fish have been focused more in the metabolic adjustments of energy reservoirs, osmoregulation, coupled acid–base respiratory trade-offs and growth in heated, cooled, hypoxic or

contaminated dwellings, and less in the effects on immune responses to such environmental insults.

Parasites also contribute to energy and nutrient flows in aquatic ecosystems, modulating host population dynamics and trophic networks, interfering with reproductive seasonality and influencing coevolving morphologies and complex lifecycles involving multiple hosts for retaliating immune strategies of antigen sensing in the host (Marcogliese 2002; Rohde 2002; Rohlenová et al. 2011). The extent of parasite biomass and communal structure is not yet well characterized, but some studies have highlighted that the effect of temperature in virulence and speciation rates in ectoparasites, or endoparasites in ectotherm species, may depend upon differences between freshwater and marine environments (Scharsack et al. 2016; Poulin 2016; da Costa and Val 2020). Temperature may also have a relevant influence in the still unaccounted importance of cryptic parasites, i.e. species genetically distinct but with very similar morphologies (Poulin 2011). Pulse warming events, short-term temperature fluctuations derived from seasonal anomalies and extreme weather related to global warming, has been shown to affect fish immune responses, habitat use and migratory adjustments due to the expansion of parasite ranges, altered life stages and increased virulence in the host–parasite trade-offs (Claar and Wood 2020).

The impact of human-induced rapid environmental changes (HIRECs) on fish immune performance is still in its infancy, and it will require an appropriate conceptual framework that may encompass the multilevel, transgenerational and overlapping influences on immune outcomes of anthropogenic and "natural" (as opposed to human-dominated), changes in aquatic landscapes (Sievers et al. 2018; Donelan et al. 2020). The effects of HIRECs on fish diversity and performance depend largely on habitat distribution, with coastal environments more prone to suffer from human-derived disturbances (Halpern et al. 2008). Human-induced alterations in aquatic ecosystems include, but are not restricted to, climate change, pollution, eutrophication, exploitation, habitat degradation, invasive species and hatchery production, inducing local, ecological and also commercial extinction of the most consumed species (McCauley et al. 2015). Coastal estuarine areas may suffer from acidification due to eutrophication, aquaculture practices, freshwater run-offs and tidal exchanges, besides the continuous increase in atmospheric P_{CO2} (Duarte et al. 2013). The impairment of connectivity networks between habitats may affect food webs and species abundance and dispersion, altering the host–pathogen cycles (Duarte et al. 2020). Albeit the modelling of the changes in climate patterns is as good as the quality of the data that validate and support the forecasting, it is beyond doubt that, for ectotherms, climate change may influence distribution patterns, species richness, genetic variation along biogeographical clines, colonization and diversification rates and immune responses to pathogen outbursts (Stanley et al. 2018; Clucas et al. 2019; Manel et al. 2020). These and other ecological constrictions limit the scope, performance and diversity of fish immune systems, in what has been increasingly recognized as a complex system of mutual interaction between the needs of immune surveillance and response, and the physical and biotic intricacies of aquatic realms. An ecological immunology approach to analyse the

evolutionary road to fish immune constructs is much needed as it may help to prevent and anticipate the changes in aquatic communities due to expanding human activities.

20.3   The Fish Approach to Immune Defence

The pathogenic load, together with the spatial and temporal heterogeneity and resilience to unpredictable changes in aquatic habitats, affects all levels of endogenous responses, from major neurosecretory and hormonal regulatory systems, to plastic behavioural phenotypes and moving population assemblages (Egerton et al. 2018; Flajnik 2018; Broecker and Moelling 2019; Guo et al. 2019). In this sense, the majority of efforts traditionally invested so far in the analysis of immune responsiveness in fish have been dedicated to describe the components of immunity in model or commercial teleost species subjected to pathogenic challenges, sometimes coupled with physiological responses to variable temperature or oxygen levels or common handling procedures in aquaculture practices. Current approaches rely on the analysis of immune genome repertoires and the development of transgenic models to elucidate host–pathogen crosstalk in immunocompromised species. However, the influence of past evolutionary events on species-specific immunity is still almost absent in these analyses (Solbakken et al. 2017). Fish are basal roots in the phylogenetic vertebrate branching and have endured a long evolutionary history of diversification and extinction cycles (Near et al. 2012) and several rounds of genome duplications (Glasauer and Neuhauss 2014). They also show extreme differences in morphology and life stories, colonization of extreme, nutrient-scarce habitats (Priede and Froese 2013; Crawford et al. 2020; Maldonado et al. 2020) or adaptive radiations in the aftermath of environmental upside downs and evolutionary transitions (Smithwick and Stubbs 2018; Ribeiro et al. 2018). All these upheavals have coalesced in a panoply of extremely diverse lifestyles, varied reproductive strategies and immune trade-offs that prevent a unified definition of common patterns of defensive responses in fish. In addition, the vast majority of fish retain a hardwired ectothermy that constricts immune function, which is why some species seem to try to become endotherms by means of metabolic and behavioural adjustments (Dickson and Graham 2004).

Broadly speaking, fish immunity encompasses three adaptive strategies evolved to cope with a microbial world, namely the approaches observed in "agnathans" (jawless fish), "chondrichthyes" (cartilaginous fish) and "osteichthyes" (bony, ray-finned fish, Actinopterygii, and lobe-finned fish, Sarcopterygii, including coelacanth and lungfishes). A detailed description of the immune intricacies of jawless and cartilaginous fish is beyond the scope of this review, and the readers are referred to several excellent reviews (Flajnik 2018; Smith et al. 2019). Nevertheless, a very brief sketch of immune features in jawless fish and sharks may be useful to illustrate the high variability of immune components described for marine and freshwater fish. Both cartilaginous and bony fish display the following traits: (1) dedicated organs (thymus, spleen) for the maturation of immune cells (generalist phagocytes, specialized B cells and T cells), (2) production of antimicrobial

proteins and mediators of immune responses (cytokines, immunoglobulins with variable domains), (3) the achievement of a reasonable high level of diversity for antigen-recognizing membrane receptors (TCRs) and immunoglobulins due to enzymatic rearrangement of immune genes and (4) the capability of internalization, processing and use of exogenous antigens using products of polymorphic gene sequences (MHCs, see below) as a means to coordinate the mutual activation and regulation of the distinct immune cellular subtypes. The more ancient jawless fish, lampreys and hagfish, lack specialized immune organs, except for the thymoid, an equivalent of thymus. They have B-cell and T-cell-mediated responses, and probably other cellular components of immune responses. They may have cytokines but lack immunoglobulins, and instead of MHC-regulated arrangements of immune receptors, they have evolved exclusive variable lymphocyte receptors (VLRs) as a means to diversify antigen recognition. Genomic analysis uncovers immune genes shared for all fish groups on a regularly basis, and a high degree of convergence is expected regarding common characteristics of cellular phenotypes and molecular mediators between agnathan and gnathostomata fish species. Additionally, at least three rounds of genome duplications have defined the expansion of the fish immune repertoire (Kuraku et al. 2009), two of them before the agnathan/gnathostomata divergence, around 500–800 million years ago (Mya), and the most recent after the split of the teleost lineage, 325–350 Mya, probably helping in their successful adaptive radiation (Glasauer and Neuhauss 2014). A fourth genome duplication event 88–90 Mya has equipped salmonids with several paralogous and duplicate genes still retained in extant species (Christensen and Davidson 2017), and, more recently, around 12 Mya, in carps (Xu et al. 2019).

Teleostei house the vast majority of extant fish (Nelson et al. 2016) and may be considered the most advanced ray-finned fish (Actinopterygii) in terms of alternate functional physiology frameworks, but it is not possible to extrapolate the immune features of teleosts to all fish. In fact, the fuzzy definition of "fishes", a term used to refer to a multiplicity of morphologies, species and taxonomic phylogenies, is still controversial, even in the phylogenomic era (Hughes et al. 2018), and confuses the description of common fish immune responses. An ever-growing number of fish genomes have been sequenced in non-model species (Buonocore and Gerdol 2016; Wcisel et al. 2017; Hara et al. 2018; Ravi and Venkatesh 2018; Smith et al. 2018), but Actinopterygii have been the object of the vast majority of functional immune studies to date. Therefore, here we will focus on teleost models to discuss the effects of environmental stressors in immune performance.

20.3.1 Teleostean Immunophysiology (I): Common Vertebrate Features

In infected or immunocompromised vertebrates, as it may happen after stress episodes, the return to original homeostatic grounds starts with the innate toolbox of local inflammatory responses. Broadly speaking, this includes a repertoire of several key overlapping

processes (Medzhitov 2008), among others: (1) on-site release of PAMPs and DAMPs (pathogen- or tissue-damaged danger-associated molecular patterns, respectively), (2) complement-mediated opsonization cascades (see Chap. 9), (3) degranulation of resident granulocytes, (4) release of antimicrobial proteins (AMPs) and pro-inflammatory/chemotactic cytokines (see Chap. 10), (5) recruitment of circulating phagocytes and cytotoxic natural killer (NK) cells to the site of infection or damage, (6) activation of hepatic acute-phase proteins and (7) antigen (Ag) recognition by dendritic cells, macrophages and other antigen-presenting cells (APCs).

The response to bacterial, viral of fungal PAMPs (see Chap. 2), is orchestrated by an array of germline-encoded soluble, membrane-bound and intracellular pattern recognition receptors (PRRs) (Takeuchi and Akira 2010), such as the highly diverse Toll-like receptors (TLR). PRRs are expressed primarily by immune cells, but also by tissue-specific epithelial/endothelial cells. Interferons (IFN) are the main mediators of antiviral responses (Secombes and Zou 2017). Pathogens can subvert the PRR recognition masking themselves with endogenous antigens, delocalizing or modifying the structure of PRRs to prevent proper bonding to antigens, changing their phosphorylation/ubiquitination features, thus targeting them for degradation, and inhibiting downstream signalling components (Majzoub et al. 2019). Exogenous and endogenous antigens are processed, fragmented in manageable peptides and presented to immune cells through highly polymorphic major histocompatibility complex (MHC) proteins (Kotsias et al. 2019). Widespread exposure to self or altered cytosolic peptides bound with MHC class I molecules in almost all cell surfaces activates cellular crosstalking and polarization of immune phenotypes, fully unrolling the inflammatory process by activation of membrane receptors of $CD8^+T_C$ (cytotoxic) cells. If the MHC I complex is impaired by viral assault, a "missing self" signal ensues and the infected cell is destroyed by NK cells. Other non-classical MHC I molecules are induced in stressed cells and contribute to the clearance by NK cells upon recognition by their fast-evolving variable receptors, a trademark of these cytotoxic cells (Parham and Moffett 2013). Extracellular antigens, once endocytosed, fragmented and bound to MHC class II molecules constitutively expressed in immune cells (mainly APCs), stimulate $CD4^+T_H$ (helper) cells that coordinate the nascent immune response. In non-APCs, such as epithelial cells and fibroblasts, interferons (IFN-γ), TLRs, TGF-β and other signalling molecules can stimulate MHC II expression during inflammatory processes, rendering the global network of interactions more complex (Neefjes et al. 2011). Several non-classical MHC molecules also bind small metabolites and participate in the editing of antigen-derived peptides, and activation of T cells and NK cells (D'Souza et al. 2019).

If the containment measures of innate immunity are ineffective, the immune response broadens, and the adaptive, highly specific immune modules, dominated by B- and T-cell subtypes, are brought into play (see Chap 4). Haematopoiesis increases, and lymphocytes with variable surface receptors begin to be mass-produced and selected for improved antigen affinity in specialized lymphoid organs, such as lymph nodes and spleen. To ensure the diversity of antigen-recognizing receptors, at earlier stages of B- and T-cell

differentiation, RAG1-RAG2 endonuclease complex helps rearrange the gene segments that encode the different Igs and TCRs, enabling the ulterior clonal selection of high-affinity receptors capable of recognizing a vast array of antigens (Ru et al. 2018).

The vast majority of T cells consist of αβT cells, which participate in the overall adaptive response to antigens, whereas the less abundant, and still less studied, γδT cells have also been implicated in antigen recognition in innate-like immunity (Rampoldi et al. 2020). Immature B cells express IgM/IgD surface receptors, and in mammals, but not in fish (see Chap. 8), if stimulated by antigens and cognate T cells, change the isotype to IgG, IgA and IgE. Once exposed to antigen, B cells also endure several cycles of somatic hypermutation (SHM) of immunoglobulin gene segments, facilitating the cloning and expansion of Ag-specific cellular populations. Once diversified, these cellular populations are confronted by follicular dendritic cells (FDCs), APCs and T follicular helper (T_{FH}) cells in the germinal centres of lymph nodes (absent in fish) and other secondary lymphoid organs. These processes mature the affinity of the differential surface receptors for the antigen in the precursors of Ig-producing B cells. The mutagenic changes in Ig genes elicited by activation-induced deaminase enzyme (AID) rearrange gene segments and, ultimately, favour SHM and immunoglobulin isotype class switch recombination (CSR), which, in turn, refine and enforce the antigen–antibody (Ag-Ab) bond, dramatically improving the overall immune response (Methot and Di Noia 2017). Once matured, B cells produce specific antibodies, whereas $CD4^+$ T_H and regulatory (T_{REG}) cells orchestrate the immune crosstalk and reactivity, and $CD8^+$ T_C cells neutralize infected cells and collaborate to the overall cytokine signalling. If effective, the adaptive countermeasures end with (1) the controlled and apoptotic-regulated clearance of activated immune cells, (2) the nesting of quiescent populations of long-lived plasma cells (LLPCs), true memory B cells and T cells and probably NK memory cells (Beaulieu 2018) that guarantee rapid responses upon re-exposure to the same antigen and (3) the clean-up of immune debris and tissue healing, mainly by specialized macrophage M2 phenotypes (see Chap. 6) and other tissue-healing cells (Yunna et al. 2020).

After immune challenge or stress, the complex intricacies of coordinated networking between all the participants at each stage of immune responses result in high time-dependent malleability of cellular phenotypic changes as defensive actions progress. All these cellular immune phenotypes, innate or adaptive, either recirculating or anchored to specific tissues, come in several forms, developmental stages and polarized functions that usually coexist spatially and functionally and can contribute to blur the distinction between innate reactivity and adaptive reactivity (Van Kaer et al. 2019). Differentiated tissue-resident macrophages, for example, are a heterogeneous composite of embryonic, steady state and adult monocyte-derived active cells that adds up to the complexity of local, tissue-specific inflammatory responses (Ginhoux and Guilliams 2016). On the adaptive side, naïve T_H cells adopt several phenotypes, T_H1, T_H2, T_H17 or T_{REG}, depending on the timely production of specific cytokines during inflammation. This differential cellular polarization may bias T_H responses towards general cytotoxicity against cancer cells or intracellular pathogens (T_H1 cells), immunosuppressive processes (T_H2 cells), intestinal microbiota

homeostasis (T_H17/T_{REG}), regulation of immune responses against self-antigens (T_{REG}) and protection against extracellular bacteria and fungi (T_H17), although there could be some functional overlap between the different T_H phenotypes (Yamaguchi et al. 2015). Both innate myeloid and lymphoid cells may display a short-term memory, antigen-independent, that enhances reactivity to repeated exposure to the same antigen. Once active, monocytes, macrophages and NK cells undergo epigenetic reprogramming that change their chromatin profiles, enhance glycolytic metabolism and increase cellular responsiveness after being immunologically "trained" (Netea et al. 2016). Overall, this suggests that it is not possible to divide the vertebrate immune responses between rapid, unspecific, early-responding innate components, and long-lasting latecomers, highly specific ones, capable of establishing a memory of recent infections. As has been recognized in the last decades, many participants of adaptive immunity in vertebrates educate, and are triggered by, the concerted action of innate immune components (Iwasaki and Medzhitov 2015) in what is now considered a continuum of progressive defensive responses, and, more importantly, a source of immune plasticity when confronted with environmental insults.

20.3.2 Teleostean Immunophysiology (II): Particularities and Drawbacks

Teleosts differ from mammalian counterparts in the organography, components, onset, duration, memory and functional effectiveness of immune responses (Salinas 2015; Geven and Klaren 2017; Secombes and Zou 2017; Flajnik 2018; Reverter et al. 2018).

The main regulatory hub and primary lymphoid tissue of both stress and immune responses in fish is the head kidney (Fig. 20.1), where mixing of neuroendocrine and haematopoietic/immune cell populations occurs, resulting in a constant molecular crosstalk, and can be considered a functional analogue of mammalian bone marrow and the adrenal gland (Geven and Klaren 2017). Fish tend to diminish the barriers between capsulated and structured organs devoted to a single function and, instead, possess multi-functional integrative organs (see Chap. 1). In this sense, in teleosts, the head kidney coordinates the neuroimmunoendocrine crosstalk derived from the innervation of lymphoid organs (Balasch and Tort 2019). Head kidney cells produce and secrete the two most relevant stress hormones after stressful stimuli: adrenaline by chromaffin cells and cortisol by interrenal cells (Fig. 20.1). Moreover, the co-localization of these two cell types enables paracrine interactions between these cells, thus enabling cross-influences (Rotllant et al. 2006). Cortisol and catecholamines are important inducers of cytokines from macrophages, as these cells have both α-adrenergic and β-adrenergic receptors (Maciuszek et al. 2019) and glucocorticoid receptors. Moreover, together with cytokines, glucocorticoids evoke a strong synergistic enhancement for most acute-phase proteins (APPs) (Bayne and Gerwick 2001). The presence of adrenergic and hormonal receptors in immune cells modulates cytokine secretion that, in turn, docks in immune receptors in neuroendocrine cells, closing the homeostatic circle (see Verburg-van Kemenade et al. 2017 for a thorough review).
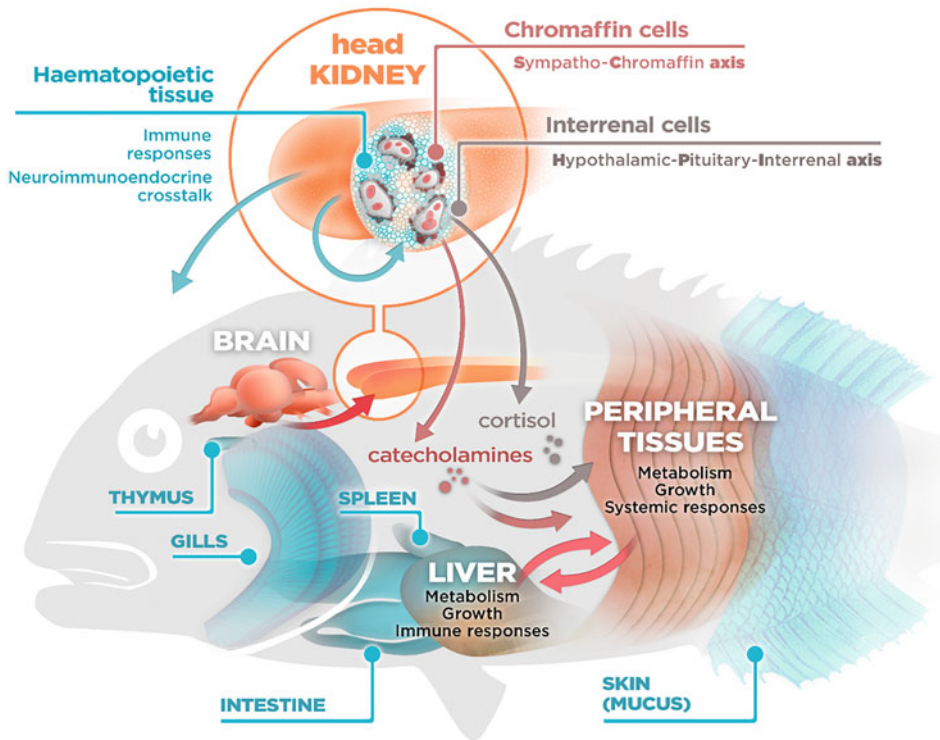
Fig. 20.1 Stress axis and immune dedicated tissues and associated organs in teleosts. Head kidney and spleen are considered the main lymphoid organs, facilitating cell trafficking and harbouring melanomacrophage centres (MMCs), involved in antigen trapping and processing. Mucosa-associated lymphoid tissues in gills, intestine and skin endure parasite attachment and ever-growing microbial communities that modify and educate host immunity. Liver produces acute-phase response antimicrobial peptides and innate complement factors. The influence of immune responses reaches the overall metabolic trade-offs and affect and is affected by the activation of several main regulatory axes, among them the catecholamine-producing sympatho-chromaffin (SC) axis, and the cortisol-producing hypothalamic–pituitary–interrenal (HPI) axis. Under stressful environmental changes, metabolic trade-offs influenced by temperature changes, parasite load and other environmental stressors may impair growth and overall allostatic adjustments

The thymus acts also as a primary lymphoid organ dedicated to the development of T cells and, as described for mammals, regresses with age, but only in some species (Bowden et al. 2005). The spleen and the lymphoid infiltrates in mucosal tissues are considered secondary lymphoid organs in an immune system that not only harbours less immune cell phenotypes and molecular effectors than mammals (Flajnik 2018) but also lacks mammalian-like highly structured intestinal lymphoid nodules, using melanomacrophage centres as surrogates of lymph nodes (Stosik et al. 2019).

Upon detection by dendritic cells, macrophages, granulocytes and IgT/Z+ B cells in mucosal tissues (see Chap. 12), clearance of undesired antigens or malfunctioning cells in

fish requires the coordinated participation of the head kidney's immune axis (Fig. 20.1), catecholamine-producing sympatho-chromaffin (SC) axis and cortisol-producing hypothalamic–pituitary–interrenal (HPI) axis (Khansari et al. 2018; Balasch and Tort 2019). Inconclusive immune outcomes require additional recruiting of cellular and molecular components of the overall defensive responses, including the hypothalamic–pituitary–thyroid (HPT) axis (Geven and Klaren 2017) or hypothalamic–pituitary–gonadal (HPG) axis and growth hormone (GH)/insulin-like growth factor (IGF) axis, especially in migratory species such as salmonids (Ueda 2019).

Overall, cellular and humoral responses in teleosts seem to follow the same pattern as in mammals (Rebl and Goldammer 2018; Smith et al. 2019). However, several mammalian-like and fish-specific TLRs have been described, being highly variable between species (Palti 2011). An illustrative example of the alternative, non-mammalian ways of pathogen sensing in fish is TLR4, an essential PRR for the recognition of bacterial lipopolysaccharide (LPS). Many teleost fish lack a functional TLR4 framework and have greater tolerance to LPS doses than mice or humans in endotoxaemic models (Swain et al. 2008). Alternative sensing pathways to LPS in transcriptomic models of *Schizothorax prenanti*, a cultured fish species in China, challenged with *Aeromonas hydrophila* and *Escherichia coli* LPS include expression of regulatory cytokines (*IL-1β, IL-10* and *IL-8*) and PRR (*TLR5, TLR25, PTX3* and *C1q*) transcripts that have been suggested to mediate the LPS responses in this teleost species (Li et al. 2020). However, the higher tolerance to LPS in teleosts remains intriguing, and, again, the microbial-rich characteristics of dwelling in an aquatic environment seem to be involved (Lieschke and Currie 2007).

All T-cell subsets (T_H, T_{REG} and T_C) seem to be present in teleosts (see Chaps. 3 and 4), but the morphological and functional description of cellular immune phenotypes in fish is still far for being complete, especially for innate lymphoid cells. Thymic homing from haematopoietic tissues and RAG-mediated selection for non-self-reactive T-cell phenotypes are believed to be similar in teleosts and mammals, but little is known about the commitment of αβ and γδ T-cell categories in teleosts (Bajoghli et al. 2019). B cells develop and mature in the head kidney and migrate to secondary lymphoid organs such as the spleen and posterior kidney, where the antigen-mediated stimulation takes place (Saunders et al. 2010). Once matured, the final plasma cell phenotype recirculates to the head kidney (Ye et al. 2011). Unlike mammals, teleosts produce only three types of immunoglobulins (see Chap. 7), IgM, the main circulating Ig, IgD and IgT, the latter more abundant in mucosal tissues, similar to IgA in mammals, and involved in the mutual regulation of complex host–microbe interaction (Zhang et al. 2010). IgD is still poorly studied, but the presence of IgD$^+$IgM$^-$ precursor B cells in mucosal surfaces suggests that, as in mammals, IgD participates in pattern recognition (Gutzeit et al. 2018; Perdiguero et al. 2019). Notwithstanding the lack of germinal centres and FDCs in fish, affinity maturation seems to be present in teleosts. Melanomacrophage centres (MMCs), clusters of melanomacrophages (MMs) enriched in melanin, lipofuscin and hemosiderin that are present in lymphoid tissues, are postulated to be the analogues of germinal centres in fish. These are sites where antigen trapping and presentation to activated IgM$^+$B cells may

enhance Ag-Ab bonding, coordinated by MMs acting as functional analogues of FDCs (Stosik et al. 2019). However, the main function of MMCs is to accumulate and destroy metabolites and discarded cells. Indeed, the highly interspecific variability and temperature sensitivity of the activation-induced deaminase (AID) enzymatic activity suggest that the maturation of affinity may not reach the levels described in mammals, where up to 1000-fold higher affinity for the antigen is seen in plasma cells relative to that of the original mature naïve B cell, compared to a 100-fold increase described for ectotherms (Magor 2015). Affinity maturation has been described recently for long-lived plasma cells (LLPCs), primarily in the head kidney but also in the spleen of channel catfish (*Ictalurus punctatus*). Upon immunization, LLPCs appear in the head kidney 4 weeks post-immunization, after activation in the spleen and other peripheral lymphoid tissues, and secrete high-affinity antibodies, with serum titres that reach a peak 6 weeks post-immunization (Wu et al. 2019). It has been suggested that secreted teleost IgM tetramers undergo variable disulphide polymerization that may also contribute to affinity maturation of antigen recognition (Ye et al. 2010). Class switch recombination (CSR) in activated B cells, a change in the constant region of the Ig heavy chain that leaves the variable region untouched but expands the immune interaction and recognition capabilities by producing different Ig isotypes, has not been described in fish (Patel et al. 2018). Overall, antigen recognition and Ig-mediated responses in teleosts lack the efficacy and diversity observed in endotherm vertebrates.

It is relevant to note that erythrocytes are nucleated cells in fish, and hence can perform gene transcription and within their transcriptome are immune-related genes. For example, RNA-Seq analysis after poly (I:C) treatment shows diverse cohorts of mRNA transcripts related to immune function in erythrocytes. Moreover, erythrocytes can express a type 1 IFN response (Morera et al. 2011) and in vitro can endocytose TNF-α and VHSV G-protein fragments (Puente-Marin et al. 2019). Therefore, erythrocytes play a role in the immune response of fish. It is not yet clear whether this is a primary or a subsidiary or complementary role, particularly under stress situations, but it should be noted that there is a huge quantity of red blood cells compared to leucocytes, so even a small individual role will have an impact in the overall immune response (Morera and MacKenzie 2011; Anderson et al. 2018).

Surprisingly, some species, including Gadiformes, anglerfish and pipefish, have lost the MHC II. The evolution and maintenance of MHC diversity in teleosts (see Chap. 11), and therefore the competence to recognize self- and non-self-antigens effectively, depend on the delicate interplay between the unavoidable requirements of physiological trade-offs in specific niches. This is guaranteed by the ecological relevance of parasite load and their intrusive abilities when confronted with mucosal barriers, and the great plasticity of immune responses in fish. The loss of MHC II pathway components in pipefishes (*Syngnathus*), for example, has been attributed to their sex role reversed parental care strategy. *Syngnathus* feature male pregnancy, housing fertilized eggs in inverted tail brood pouches, feeding the developing embryos through placenta-like organs that allow for both the transmission of oxygen and also immune components. Gene expression studies of

Vibrio spp. and *Tenacibaculum maritimum*-challenged pipefish suggested differential parental immune priming of F1 and even F2 offspring, with parent males influencing strongly on offspring innate immunity and complement system components (Beemelmanns and Roth 2016; Beemelmanns and Roth 2017). Interestingly, sex-specific methylation patterns of immune genes were also observed, which are influenced by sex in other fish (Caballero-Huertas et al. 2020) and may be related to predictable, and stable parasitic load pressures over time. As described for Gadiformes (see below), in addition to the loss of MHC II, and CD4 components, diversification of MHC I pathway genes was also found in pipefish. However, MHC I transcripts and pro-inflammatory- and adaptive-related immune genes were found to be downregulated (Roth et al. 2020). This indicates, as the authors suggest, a convergent strategy to minimize the perils of embryo rejection as described for pregnant mammals, in which T_{REG}-mediated suppression or downregulation of MHC I and MHC II genes in the placental barrier ensures no immune reactivity to the antigens of the other parent (Prabhu Das et al. 2015).

At early stages, the development of primary and secondary lymphoid organs, together with the production of associated B/T cellular phenotypes, depends on environmental variables (such as temperature and food abundance) and varies greatly on a species-specific basis. Small eggs correlate with shorter yolk sac stages and fast hatching, but spleen, thymus and the haematopoietic/immune cellular subtypes produced in the head kidney appear several days after hatching, during the fast growth period characteristic of teleost larvae (Falk-Petersen 2005; Zapata et al. 2006). During the yolk stage, maternal transference of immunoglobulins, components of the complement system and other anti-microbial proteins (AMPs) help the developing embryo to keep pathogens at bay (Swain and Nayak 2009; Roth et al. 2018). This transgenerational immune priming is a strategy shared also by several invertebrate taxa (Tetreau et al. 2019). In addition, as suggested by transcriptomic analyses of immune gene expression across several stages post-hatching in the common sole (*Solea solea*), PPR sensing is also enhanced at hatch and first feeding, whereas increased abundance of MHC and TCRs transcripts correlates with the maturation of lymphoid organs during the metamorphosis (Ferraresso et al. 2016). The same study failed to detect RAG1 or CD4^{+} and CD8^{+} markers, suggesting that at the end of metamorphosis T-cell differentiation is still incomplete in this species. In fact, the maturation of immune organs constricts the efficacy of temperature-dependent antiviral and pro-inflammatory responses during larval stages, as demonstrated for zebrafish (*Danio rerio*) and European eel (*Anguilla anguilla*). This would impair the immune response to pathogens (Dios et al. 2010; Miest et al. 2019), even in anadromous and catadromous species undergoing the metamorphosis-like rearrangements prior to migration (McMenamin and Parichy 2013; Yada et al. 2018). Juvenile Atlantic salmon (*Salmo salar*) enduring the osmoregulatory and metabolic strengthening from the smoltification process prior to the downstream migration to open sea usually are affected by immunosuppression (Johansson et al. 2016). Hence, thermal stress may modify the timing of migratory behaviour, biasing metabolic, growth and immune trade-offs, ultimately changing the structure and composition of local age classes in the population (Cline et al. 2019). The

reliance on innate/unspecific immunity during the first stages of development renders fish larvae more prone to high mortalities, not only during the yolk phase, when high mortalities are expected, but also during the juvenile and early adult stages, that are more sensitive to stressful changes in environmental variables due to the incomplete maturation of adaptive defence mechanisms.

Overall, ecological factors limit the development and the functional performance of mature immune systems in fish, determining the extent to which individuals may cope with complex environmental stressors. In aquatic dwellings, immunity serves as a high-demanding metabolic sieve to screen for opportunist and virulent pathogens that crave for mucosal epithelia to attach in a seasonal, cyclic way, influenced by rises in temperature in a system dominated by ectotherms.

20.4 The Scalability of Stress Responses in Fish: From Stressed Cells to Systemic Immunomodulation

The processing of relevant information by the components of the immune system requires metabolically expensive parallel and distributed complex computation (Cohen and Efroni 2019) to solve the related problems of identifying cellular and humoral friends and foes, inflammation management, tissue repair, cancer control and, especially, symbiont housing, leaving sticky notes of the immune progression in the form of specialized receptors in neuroendocrine cells. In this computational sense, the overall performance of immune activation resembles those of the neuroendocrine machinery in terms of complexity and scope, and can be considered as an emergent feature based upon a plethora of underlying local cellular and molecular interactions and cross-recognitions between modular (i.e. classical innate and adaptive) components (Sotiropoulos and Tsihrintzis 2017). All vertebrate immune systems can be modelled as problem-solving algorithms dedicated to live, learn and remember the stressful changes in the pathogenic and xenobiotic environment (Fig. 20.2).

Fish may endure resilient human-induced environmental changes and thrive throughout sustained global pathogenic blooms, marine heating or acidification in part because of in-built plastic neural and behavioural adaptive mechanisms (Ebbesson and Braithwaite 2012; Maruska et al. 2019). However, these capabilities tend to be highly species- and niche-specific, and strongly constricted by each particular evolutionary history of physiological regulatory systems (Lee 2006; Solbakken et al. 2017). In this sense, higher lifestyle diversity and niche occupation may be beneficial in altered ecosystems, but the particular idiosyncrasies of each species or individuals constitute a major drawback for establishing a common unified framework to describe, evaluate and palliate the effects of compromised immune performances in the context of neuroendocrine responses (Balasch and Tort 2019; Taborsky et al. 2021).

Although a precise definition of stress is difficult due to the number of aspects associated with this concept, there is a general agreement in considering stress as an altered situation
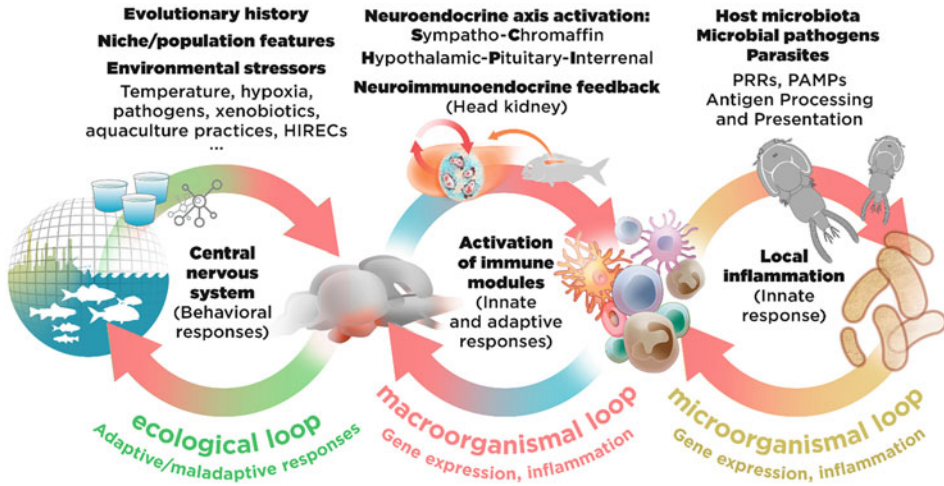
Fig. 20.2 Nested loops of neuroimmune control in fish. A series of nested loops participate in the mutual regulation of neural and immune responses (Irwin and Cole 2011). In fish, environmental stressors activate the hypothalamic–pituitary–interrenal axis (HP), the sympatho-chromaffin (SC) axis, and the haematopoietic/immune tissue in the head kidney (HK). The crosstalk between chromaffin, interrenal and haematopoietic cell populations in the HK guarantees a constant neuroimmunoendocrine local regulatory feedback that helps in the activation of immune modules. The transcriptional outcome of the inflammatory processes depends on the intensity of the environmental insults, and the species-specific determinants of the allostatic processes in the organism (extrinsic control of the immune response), as well as the local recognition of soluble or membrane-bound evolutionary conserved pathogen-associated molecular patterns (PAMPs) by means of pathogen recognition receptors (PRRs) in host cells (intrinsic control of immune local inflammation). Once started, inflammation may progress to systemic immune responses, recruiting cells and tissues to mount an adaptive immune response that, in turn, may alter the behavioural phenotype of stressed organisms. Several subloops (not shown in the figure), such as the crosstalk between innate and adaptive immune components, or the delicate equilibrium between host symbionts and mucosal immune surfaces of gills, gut, skin and nasopharyngeal spaces contribute to the fine regulation of neuroimmunoendocrine circuitry in fish

of the organism from its normal physiological scope as a result of a real or symbolic challenge. The stressor is defined as the challenging agent causing such a response. Stress is a universal phenomenon, and thus, any living organism may experience situations that cause these reactive or compensatory physiological responses, the so-called, stress response. It should be remembered that, since all organisms are subjected to challenges, all organisms experience stress responses and it is therefore observed that some of the basic components of the stress response have been maintained in all living organisms, and consequently, different taxa show similar molecular components and pathway mechanisms. In most cases, one can identify a specific number of molecules mediating the stress response that are common among animals. For instance, a group of these molecules, namely corticosteroids, adrenaline or cytokines, do exert the same networking

function in the stress response in all groups of vertebrates (Hau et al. 2016; Miles et al. 2019). Thus, although the stress concept was defined for mammals by Hans Selye in the last century, it is currently applied to all types of animals, plants and even to different levels of organizations (cell stress, organ stress and whole organism).

Stressed cells share common activation pathways to limit molecular damage and preserve macromolecular structure (and, hence functionality) by maintaining a robust proteostasis network of chaperones, components of the proteasome complex and other mediators that help to synthesize, fold, traffic and degrade proteins, guaranteeing a low level of misfolded or aggregated molecules in the proteome (Sala et al. 2017). Among pre-transcriptional responses, chromatin remodelling involves control over transcription, as there are a number of phenomena that will modify the translation of messenger RNA, such as alternative splicing, or gene silencing by miRNA. Regarding the post-translational response, the ubiquitination system uses small proteins that covalently modify other proteins in cells with consequences in transcription, proliferation, DNA repair, protein degradation and nuclear localization (Mazzucotelli et al. 2008). Under stress conditions, altered or wounded cells, ubiquitins upregulate the NKG2D (natural killer group 2, member D)-activating receptor in mammals, through high levels of MIC ligands (MHC class I polypeptide-related) and activating NK cells and T cells that, ultimately, eliminate altered cells (Stern-Ginossar et al. 2008). The evolution of metazoan *bauplans* requires the coordinated participation of several cell lineages across different tissue and systemic regulatory networks, which in turn rely on paracrine crosstalk to transfer the cellular distress between nervous, endocrine and immune systems. Unsurprisingly, some components of the proteostasis network, and also several intracellular pathways that allow for their activation, are shared between stress and immune main activation axis in vertebrates (Miles et al. 2019). At the cellular level, the response of the organisms to any type of tissue damage and infection will involve immediate-specific reactions in order to repair the damage, promote wound healing, protect against invading organisms and contribute to host defence mechanisms, in particular the innate immune response. These rapid reactions involve a number of specific proteins, the acute-phase proteins involved in the so-called acute-phase response, APR, mainly produced in the liver that may enhance or depress inflammatory responses (Black 2003). Some of these molecules involved in cell stress responses are well conserved through evolution and have been used as molecular indicators of any kind of stress including immune stress. Therefore, such proteins would be involved in the regulation of both cell immunity, cell damage or altered metabolism. Among the specific proteins associated with immunity and stress is NF-kβ, a highly conserved family of related protein complexes in metazoans (Ghosh et al. 1998) that, once activated by bacterial or viral antigens, activates or represses hundreds of genes in stress-related immune responses (Zhang et al. 2017), including inflammation, cell migration, cell repair and metabolic activation. Map kinases (MAPKs) are signal transduction mediators that are central for the correct function of many aspects of cell physiology, including cell defence against pathogens. MAPKs also activate SAPKS or JNK after alterations in cell osmolality, stress stimuli, inflammatory signals, variations in the level

of reactive oxygen and other signs of cell stress associated with defence and immunity (Kyriakis and Avruch 2012). Another kinase, AMPK, is activated when there is a low level of intracellular ATP, cell growth arrest and biosynthetic reduction. Its activation induces glucose and fatty acid uptake and oxidation to recover cell energetics in a subset of lymphocytes, T regulatory cells, that, together with M2 macrophages, the alternative anti-inflammatory phenotype of classically activated M1 macrophages (Locati et al. 2020), regulate the termination of inflammation (Michalek et al. 2011).

Among stress proteins, one group that has been widely associated with stress is the heat shock protein group (HSP), a superfamily of proteins that have been well conserved through evolution, thus present in bacteria, fungi, plants and animals (Feder and Hofmann 1999; Timperio et al. 2008). Although they were discovered after heat shock treatments, they are induced by a huge variety of environmental stressors. HSP and other stress-related proteins work as chaperones, responsible for maintaining the integrity of the molecules in the cell that are transcribed in response to stressful stimuli and they are conserved in all domains of life, but they can also act as DAMPs, damage-associated molecular patterns that initiate inflammatory processes (Schaefer 2014). In mammals, several HSP families have been described to activate immune responses, participate in the pro-inflammatory and apoptotic responses to viral infection, usually enhancing the immune reactivity, but also helping to replicate or assembly the viral particles during dysregulation episodes in HSP function (Wan et al. 2020). The production of hepatic C-reactive protein (CRP), an AP protein, stimulated by an inflammatory cytokine, interleukin 6 (IL-6), has also been associated, in addition to immune responses, with fatty acid metabolism in muscle, feeding, regulation of adipose tissue and overall metabolic maintenance (Del Giudice and Gangestad 2018), processes that may interlock in part during stressful outcomes and suggest a multifactorial role of immune mediators in stress-related metabolic trade-offs. For example, in mammals, chronic stress enhances several inflammatory cytokines, including IL-6 and CRP, probably by means of desensitization of immune cells to the effects of glucocorticoid inhibition (Cohen et al. 2012).

20.4.1 The Central Role of Glucocorticoids

As chemical messengers secreted to blood mainly from the pituitary and head kidney, fish hormones are principal mediators of the systemic stress response but also influence the immune system. Their effects normally take some time because hormones have to reach the receptors in the target tissues that subsequently regulate processes like gene expression, morphological changes or protein synthesis. Nonetheless, it has also been shown that some hormones can be produced locally, which enables them to act acutely through a paracrine process, and therefore have no delay due to transit time by the bloodstream (Calisi and Saldanha 2015). Among the many hormones activated after stress, glucocorticoids or corticosteroids are crucial for modulating the response of the immune system, in addition to also modulating many other functional processes, including metabolism, development or

behaviour. Thus, following stress challenges, glucocorticoids will affect multiple physiological, behavioural (Kelly and Vitousek 2017) and life-history (Crespi et al. 2013) elements as components of the homeostatic response. Hence, circulating glucocorticoids represent a plastic phenotype coming from a single genotype that allows individuals to release different concentrations of these circulating messengers depending on the varying environmental conditions and individual perception (Romero and Gormally 2019). One of the sites where endogenous glucocorticoids exert powerful effects is on inflammatory and immune processes. Nevertheless, as pointed out by evolutionary and comparative biologists, in terms of the overall understanding of the glucocorticoid effects, it becomes paramount to quantify the individual variation of these mediators, as this would help to evaluate the current variability in immunity, behaviour, physiology and overall response performance (Guindre-Parker 2020). As a consequence, the recognition of such variability has shown that analysis of cortisol alone is insufficient when used as a single bioindicator to measure the overall stress response and its consequences (Romero and Gormally 2019; Telemeco and Gangloff 2020).

Cortisol modulation entirely depends on the presence of glucocorticoid receptors in the cells. The pleiotropic effects of glucocorticoids will then largely depend on the extension of binding to the different glucocorticoid receptors found in fish tissues (Landys et al. 2006). Thus, it is relevant to point out several features that are important regarding cortisol receptors in fish. First, fish present two glucocorticoid receptors (GR1 and GR2) and one mineralocorticoid receptor (MR) (Faught and Vijayan 2018). Second, alternative splicing variants of glucocorticoid receptors have been found under stress conditions (Romero et al. 2020). Third, receptors are ubiquitously expressed in all tissues including immune tissues. Therefore, the receptor-mediated response is complex in fish and for other vertebrate species.

Altogether, thanks to their ubiquity and complexity, cortisol receptors bring a high plasticity in terms of regulation of physiological and immune responses after stress. For example, high-affinity and low-capacity mineralocorticoid receptors are sensitive to relatively low concentrations of circulating cortisol that will be helpful in regulating metabolism and energetics, whereas high cortisol concentrations in the blood will initiate acute alarm responses including immune signalling (Landys et al. 2006). Receptor type, receptor density, time course and transcriptional effects of circulating glucocorticoids in the blood will involve differential effects across tissues and environmental contexts, thus modulating the action of cortisol and therefore the influence on the immune response (Breuner et al. 2013; Guindre-Parker 2020). Two mechanisms of action have been described after activation of glucocorticoid receptors. First is the genomic signalling, which takes hours to days to express the corresponding effects (Nicolaides et al. 2010). Second, the non-genomic signalling, a rapid mechanism taking only seconds to minutes, that activates plasma membrane proteins using second messengers such as cytoplasmic free calcium (Panettieri et al. 2019; Johnstone et al. 2019; Faught and Vijayan 2019). These signals will modulate the transcription of key genes of the pathways concerned with the generation of immune responses.

Once glucocorticoid receptor signalling is activated, some pathways of innate immunity are enhanced, but most pathways of adaptive immunity are suppressed (Cain and Cidlowski 2017). Low concentrations of endogenous corticosteroids upregulate PRRs, thus sensitizing the innate immune system through cytokine receptors and complement factors, thus allowing the induction of acute responses to danger signals (Cain and Cidlowski 2017). High concentrations of glucocorticoids, by contrast, suppress signals that are mediated by PRRs and cytokine receptors, thereby preventing excessive and/or prolonged immune responses. The inhibition of the transcription of immune response genes is mediated by three mechanisms. First, suppression of the glucocorticoid receptor to gene promoter sequences, second, induction of glucocorticoid receptor-mediated transcription of anti-inflammatory genes (such as NF-κβ-IA) and, third, non-genomic antagonism of pro-inflammatory transcription factors (such as NF-κβ) or via protein–protein interaction (Verburg-Van Kemenade et al. 2009). It should also be noted that the reverse signalling pathway has been observed, whereby GR expression is affected by immune stimulation. Thus, injection of LPS increases expression of GR in the spleen of gilthead sea bream (Acerete et al. 2007), and in common carp, GR1 expression in peritoneal leucocytes increased after 1 and 2 days of zymosan treatment (Stolte et al. 2009).

In addition to the modulation of inflammation, not only the effects of glucocorticoids on the immune system are pleiotropic and varied, but also the effects depend on the specific cell or tissue. They mediate antiviral responses including signals that are induced by affected host cells, such as necrosis or apoptosis to generate an enhanced immune gene transcription response. In addition, environmental information reaching the brain allows initiation of immune response programmes via hormones and neurotransmitters in order to mitigate autotoxic risks associated with excessive signalling through enhanced cytokine activation (Verburg-van Kemenade et al. 2011). Thus, it has been shown that glucocorticoid treatments at low concentrations or concentrations that do not involve a significant systemic challenge can enhance inflammatory responses. At higher concentrations, glucocorticoids result in suppressive effects through cytokine signalling, for instance, inhibiting the production of B cells and T cells (Cain and Cidlowski 2017).

The suppressive effects of glucocorticoids have also been shown under in vitro experiments: cortisol in vitro has been shown to reduce phagocytosis in common carp, tilapia and silver sea bream head kidney leucocytes (Law et al. 2001). It also inhibits respiratory burst activity, phagocytosis and chemotaxis dose-dependently in a goldfish macrophage cell line (Wang and Belosevic 1995). Cortisol also decreases respiratory burst activity in sea bass (Vizzini et al. 2007) and sea bream leucocytes (Esteban et al. 2004). Glucocorticoids upregulate IL-10, IL-4 and TGF-β production but downregulate IL-12, TNF-α, and IFN-γ (Verburg-van Kemenade et al. 2011). In vitro cortisol treatment of head kidney leucocytes significantly depresses phagocytosis, chemotaxis and respiratory burst activity in carp, tilapia and silver sea bream (Wang and Belosevic 1995; Verburg-Van Kemenade et al. 2009). Decreased respiratory burst activity has also been observed in sea bream head kidney leucocytes (Esteban et al. 2004). Additionally, cortisol inhibits the LPS-induced expression of serum amyloid protein (Fast et al. 2002; Stolte et al. 2006),

inhibits the proliferation of monocytes/macrophages (Pagniello 2002) and induces apoptosis in silver sea bream and Atlantic salmon macrophages isolated from stressed fish, which also show decreased survival when exposed to *Aeromonas salmonicida* (Fast et al. 2008).

Recently, it has been shown that glucocorticoids also appear to be involved in the polarization of macrophages in fish (Maciuszek et al. 2019), which would explain the contribution of cortisol in the regulation of the macrophage after stress. After pathogen challenge, LPS treatment or, after stress, macrophages polarize inducing an increase in specific cytokines such as TNF-α, which will regulate the resolution of inflammation. Thus, stimulated monocytes produce 11β-HSD1 that converts inert internal cortisol to active internal cortisol, which plays a key role in regulating polarization by promoting the transition from M1- to M2-type macrophages (Thieringer et al. 2001; Maciuszek et al. 2019). Macrophages initiate the immune reaction for pathogen eradication as polarized M1 macrophages under the influence of IFN-γ and/or LPS, but for the modulation of this reaction and for tissue regeneration/wound healing, the polarized M2 macrophages are needed, which appear upon IL-4 or cortisol stimulation.

Although less studied, immune modulation has also been found in the adaptive arm of the immune system after stress. Corticosteroids regulate adaptive immunity by inhibiting lymphocyte activation and promoting lymphocyte apoptosis. In carp, in vitro stimulation with cortisol reduced IgM secretion by head kidney cells, spleen and blood lymphocytes (Saha et al. 2004). In vivo, thermal stress treatments induced decreased antibody responses after immunization (Verburg-van kemenade et al. 1999), inhibition of proliferation and induction of lymphocyte apoptosis (Saha et al. 2004).

Nevertheless, not all effects are suppressive. Interestingly, for instance, neutrophilic granulocytes remain protected and they do not show decreased numbers after acute stress or glucocorticoid treatment: while a significant lymphopenia is observed after stress treatments, a significant increase in promyelocytes and myelocytes as well as metamyelocytes and mature polymorphonuclear neutrophilic granulocytes takes place (Wojtaszek et al. 2002; Engelsma 2003). Therefore, a dual-cell response has been observed depending on the leucocyte type. As neutrophilic granulocytes are of great importance to the first line of defence, in particular for the phagocytic response, it would be dangerous to leave the whole immune system without a fast active response. Therefore, granulocytes would be beneficial in situations when pathogens may attack an animal subjected to acute stress or injury, having the other responses in a depressed status.

20.4.2 The Neuro-Immune Circuitry Under Stress

In fish under inflammatory episodes, interaction between the neuroendocrine and immune system is always taking place and glucocorticoids are one of the regulators of such inflammatory responses through programming of macrophages. As a consequence, a regulatory balance between pro-inflammatory and anti-inflammatory actions mediated by glucocorticoids is customary. Inflammatory reactions have to be carefully controlled, as

high concentration of pro-inflammatory cytokines or the prolonged induction of these cytokines, reactive oxygen species or nitric oxide may be detrimental for host tissues. Glucocorticoids can modulate an excessive inflammatory reaction. Conditions that are associated with acute or chronic stress may either suppress or potentiate control pathways leading to disease progression through modulation of systemic or local pro/anti-inflammatory cytokines and mediators and, consequently, the Th1/Th2 (T helper cells) balance (Verburg-Van Kemenade et al. 2009). Thus, during the activation of the systemic stress response, the immune and inflammatory mechanisms are modulated towards induction of a Th2 shift. In this way, the system protects the organism from excessive activation of Th1 pro-inflammatory cytokines (Calcagni and Elenkov 2006) that could end up with a cytokine storm. Corticosteroids are also able to inhibit inflammation by decreasing signal transduction downstream of PRRs, cytokine receptors and high-affinity IgE receptors (Fce receptors).

In addition to the global modulatory effect of glucocorticoids, a second pathway mediated by the sympathetic nervous system also contributes to the modulation of pro-inflammatory and anti-pathogen programmes of the immune response (Fig. 20.1). Therefore, the regulation of the immune response becomes more complex since activation or deactivation of immune response genes is conditioned by both external influences driven by neural sensors and brain pathways, and internal factors such as cell damage or pathogenic alterations. Furthermore, it should be remembered that the interaction is reciprocal; i.e. regulation of neural activity is modulated by immune response activity. Other important factors such as biological rhythms, previous experience or time course are also processed primarily through the brain and neural circuits, thus influencing the immune response. As the regulation of immune defence in complex organisms such as vertebrates including fish is exerted through leucocytes, such cells will integrate the influences coming from intrinsic immune-related inputs associated with the interaction with microorganism invasion, and the extrinsic inputs derived from the coordinating role of the brain. Hence, in both mammals and fish, catecholamines directly affect immune responses.

Activation of the sympathetic nervous system has been found to alter the production, release and circulation of leucocytes, through upregulation of myelopoiesis, activation of haematopoietic stem cells, NK cells and release of neutrophils and monocytes from the spleen. One example of this crosstalk is the brain-mediated suppression of the sickness and depressed status or the immobilizing behaviours following inflammation, as a way to facilitate other urgent responses such as fight-or-flight behaviour in order to avoid predation or aggression. So far, only a limited number of studies concerning the effects of catecholamines on the expression of inflammatory mediators have been performed compared to studies on glucocorticoids. In carp, secretion of adrenaline reduced the percentage of monocytes/macrophages at the site of inflammation after induced peritonitis while maintaining the total number of leucocytes, which may be related to elevated apoptotic activity and a reduction in mature monocyte/macrophage populations in the peritoneum (Kepka et al. 2012). Stress-related hormones, and particularly adrenaline, modulated the expression of pro-inflammatory and anti-inflammatory cytokines in cultured sea bream

leucocytes (Castillo et al. 2008). Whereas cortisol reduced the expression of the assessed cytokines, the effects of adrenaline were not general, less evident and time-dependent. Noradrenaline via stimulation of β-adrenergic receptors modulated gene expression of leucocytes, associated with the signalling cascade of second messengers such as adenylyl cyclase, cyclic AMP and protein kinases. After β-adrenergic signalling, the transcription of IL-4 and IL-5 (Th2 cytokine genes) is stimulated in lymphocytes, whereas the expression of IFN-γ and IL-1β (T1 genes) is suppressed. Thus, biogenic amines not only modulate the adaptive immune response but also can affect innate response programmes, such as suppression of antiviral type I IFN-mediated responses and upregulation of pro-inflammatory cytokine genes, such as IL-1β, IL-6 and TNF (Verburg-Van Kemenade et al. 2009). In addition, it should be noted that catecholamines may act as glucocorticoid secretagogues in the head kidney interrenal tissue. As demonstrated in sea bass (Rotllant et al. 2006), an intracellular adenylate kinase pathway after β-adrenoreceptor activation leads to increased cortisol production. Thus, additional regulation of immune function by adrenaline through cortisol increase can be induced.

In fish, adrenergic agonists decreased phagocytosis of fish macrophages (Roy and Rai 2008). Furthermore, adrenaline and isoproterenol (adrenaline receptor agonist) reduced the production of reactive oxygen species (ROS) in rainbow trout (*Oncorhynchus mykiss*) pronephric phagocytes (Flory and Bayne 1991), while noradrenaline promoted the respiratory burst in *O. mykiss* and *Channa punctata* leucocytes. Both ligands generated this effect via adrenergic receptors. In vitro administration of adrenaline reduced the synthesis of ROS and nitric oxide, while enhancing arginase activity in carp phagocytes. Furthermore, in vitro adrenaline inhibited the expression of pro-inflammatory cytokines, chemokines and their receptors. It was therefore hypothesized that adrenaline will downregulate phagocyte skewing towards innate polarization (Kepka et al. 2012). Innervation of lymphoid tissue has been found in the spleen of Coho salmon (*Oncorhynchus kisutch*), where nerve fibres are associated with the vasculature and the MMCs. Moreover, immune cells express receptors for neurotransmitters, including adrenergic receptors. So far, adrenergic receptors have been sequenced in zebrafish, goldfish, trout and catfish leukocytes (Kepka et al. 2012).

Regarding brain structures, the blood–brain barrier is similar in fish compared to mammals, showing both molecular and functional similarities, as observed in studies on *D. rerio* (Jeong et al. 2008). So, the fish brain would be accessible or sensitive to cytokines or other mediator molecules induced by cytokines. However, although the cytokine receptor IL-1RI mRNA was found in the preoptic area of carp brain (Metz et al. 2006) it is not clear whether IL-1β or other important cytokines from outside the brain interact at the brain level, since there are large and hydrophilic molecules that are unlikely to pass through the blood–brain barrier by passive diffusion. Prostaglandins could be the mediators, as they are smaller, lipophilic and neuroactive (Maier 2003).

Evidence suggests that signalling immune mechanisms to the brain in fish may also present high similarities to mammals. It has been proposed that the vagus nerve could serve as a cytokine-to-brain communication route (Maier 2003). Nonetheless, as stressors can

induce the increase in peripheral cytokines by the activation of systems such as the noradrenergic pathway, these in turn may lead to increased brain IL-1β via one of the immune to brain routes. Again, few studies have investigated the signalling routes from peripheral blood molecules to the brain, and so, the role of cytokines in the central regulation of the stress reaction and HPI and sympatho-chromaffin (SC) axes activation in fish is not well defined. Cytokine modulation has been shown by adrenaline in fish (Khansari et al. 2017a, b), which could induce the activation of signalling pathways to the brain. Within the brain, pro-inflammatory cytokines reduce the activity of neurotransmitters such as noradrenaline, dopamine and serotonin, which will significantly determine the modulation of behavioural patterns (Weber et al. 2015). Moreover, cytokines activate several other signalling pathways into the brain to integrate both peripheral pro-inflammatory and antigenic signals with physiological and behavioural responses, such as fever, aggression or social interaction. All these mechanisms will work together under stress episodes to integrate the physiological and behavioural response with the necessary protective reaction of immune cells.

Finally, other types of indirect regulation can occur in fish, for instance associated with the connection between the gut and the brain. It has been shown both in mammals and in fish that information by chemical signals is taking place between both organs. Different strains of Gram-negative bacteria are particularly responsive to catecholamines (Butt and Volkoff 2019). Many other hormones are concerned regarding stress episodes and endocrine influences. Therefore, functions like reproduction or growth will be also affected since the neuro-immuno-endocrine interaction is effectively triggered. A clear case study is the Sockeye salmon (*Oncorhynchus nerka*) in which degeneration of a number of glands and organs has been observed associated with very high levels of steroids and the loss of immunocompetence, particularly innate responses, during the migration period (Dolan et al. 2016). Cortisol and other reproductive steroids divert energy from several biological processes including immune functions to mobilize energy that ensures the fish are able to spawn. Sex steroids have also been found to modulate cortisol production in the interrenal of salmonids (McQuillan et al. 2003). Other hormones are released to the circulation after stress, although they do not show the ample consequences of corticosteroids and catecholamines (Yada and Tort 2016). For instance, the teleost CRF hormone family is tightly associated with immune responses against microbial pathogens. In goldfish (*Carassius auratus*) and tilapia (*Oreochromis mossambicus*), brain CRF expression is increased following immune stimulation (Volkoff and Peter 2004; Pepels and Balm 2004). Urocortin, a neuropeptide belonging to the CRF family of hypothalamic hormones, induces changes in many peripheral tissues such as heart, kidney, skin, muscles, spleen and immune cells including macrophages, fibroblasts, lymphocytes and mastocytes in which its receptors CRF1R and CRF2R are highly expressed (Choy et al. 2020). Urocortin has also been shown to help in the regulation of inflammation, interacting with IL-6 and cytokine production, promoting macrophage phagocytosis and bacterial killing, and inducing antimicrobial activity against Gram-positive and Gram-negative bacteria in mammals (Campos-Salinas et al. 2013), thus reducing bacterial burden. In addition, peripheral

secretions of urocortin are involved in modulating the peripheral immune response by acting on specific receptors in different populations of immune cells to produce a wide range of effects (Dermitzaki et al. 2018).

20.4.3 Metabolic Trade-Off in Stress-Related Immune Responses

A relevant component of the stress response in animals including fish is the energetic component. Several authors have previously described such an energetic approach by defining the concept of allostatic load, i.e. the fact that alterations in the homeostasis of the animal will produce a cost in energetic terms that will have to be paid back in order to maintain the metabolic and physiological equilibrium, either in the short term or in the longer term (Romero et al. 2009). Thus, any surplus in energy expenditure devoted to overcome the stress situation will generate compensations associated with disposal of energetic resources, otherwise used for other purposes. This compensation may affect the efficacy of some functions, in particular immune induction and cell proliferation, which are highly energy-demanding: in mammals, under hypoxic (1–4% oxygen) conditions, T cells cease to proliferate, cytokines are not produced, and even granulocytes that depend on anaerobic glycolysis may be impaired (Ohta 2018). Resting immune cells, such as circulating monocytes, memory T cells, plasma B cells and their naive phenotypes, tend to rely on minimal metabolism fuelled by oxidative phosphorylation, low-level glycolysis and fatty acid oxidation, but once activated during inflammation, switch to metabolic reprogramming that translates in enhanced glucose uptake, aerobic glycolysis and synthesis of fatty acids (Gaber et al. 2017). This sustains proliferation, clonal expansion, chemokine and cytokine release, and regulation of lymphoid lineages during stress-derived pro-inflammatory processes, controlled by the activation of the hypoxia-inducible factor 1α (HIF-1α) and mTOR pathways, whereas AMP activation results in anti-inflammatory onsets that inhibit mTOR signalling and reduce cell responses (O'Neill and Hardie 2013). Overall, mounting a sustained inflammatory response increases the basal metabolic rate (BMR) by an estimate of 30–50% in homoeothermic vertebrates, with half of the energetic requirements dedicated to produce the hepatic acute-phase response (Lochmiller and Deerenberg 2000; Straub et al. 2010). In fish, vaccinated rainbow trout may endure a 20% increase in BMR over the course of 1 month (Ackerman et al. 2000; Skinner et al. 2010), whereas E. coli lipopolysaccharide (LPS) elicited a transient (48 h) increase in BMR in mosquitofish (Gambusia holbrooki) to overcompensate for the inflammatory response (Bonneaud et al. 2016). Interestingly, a recent study about the impact in juvenile O. mykiss of several stressors failed to show a strong correlation between metabolic and immune trade-offs (Wernicke von Siebenthal et al. 2018). The authors assessed the effects on resource allocation in trout enduring limited food availability (thus mimicking the seasonally scarcity of resources in the original habitat), parasitic infection by Tetracapsuloides bryosalmonae, a myxozoan parasite that causes proliferative kidney disease (PKD) in salmonids (Sudhagar et al. 2019), and exposure to ethinyloestradiol (EE2), a common

endocrine disruptor (Aris et al. 2014). The compensatory responses favoured the production of immune mediators in infected fish, but also the growth of immune organs in the resource-depleted experimental group, albeit with little metabolic trade-offs between EE2-induced vitellogenesis, infection and growth. These and other results indicate the importance of metabolic plasticity in acute vs chronic inflammation, but also the complex intricacies, still unresolved, of the species-specific combined effects of the type and dosage of the stressor in fish, even if the ecological niche or population specificities are considered.

20.5   Immune Futures: A Glimpse of the Complexities of Environmental Influences in Stress-Related Immune Responses

Searching for a conceptualization of the unavoidable scalability of stress-related immune responses and mechanisms across cells, tissues, organs, individuals and ecological assemblages, several authors have proposed theoretical approaches to the whole concept of biological stress, such as the control theory model (Del Giudice et al. 2018) based on the regulatory mechanisms to recover physiological balance, or the damage fitness model (Wada and Heidinger 2019; Breuner and Berk 2019), based on the mechanisms to avoid or recover from damage and maintain the overall health (Romero 2004). However, the mismatch between the multiple dimensions of the physiological response and the individual tools and indicators used to quantify and evaluate such responses makes it difficult to obtain fine-grain resolution of such multilevel theoretical approaches required for analysing the complexity of real-world scenarios (Telemeco and Gangloff 2020). Moreover, even if the effects of stress-related molecular mediators on the susceptibility to diseases may be similar in metazoans (Costantini et al. 2011), the secretory patterns of the same molecules that are the trademark of stress overtaking organism homeostasis in vertebrates, such as corticosteroids, are highly variable between sexes, populations, species, life-history strategies, lifecycles, social status and biotopes (Breuner et al. 2013; Hau et al. 2016), impairing the formulation of a cohesive conceptualization of the coupling of stress responses to environmental changes. Defining the factors that constrict the immune features and capabilities of fish enduring unexpected and persistent stressors in ever-changing environments demands a multilevel approach based on the evolutionary history of each species (Fig. 20.2). As described elsewhere, such *stressotopes*, adaptive scenarios with variable but measurable selective pressures over multiscale immune responses, niche-specific and capable of generating allostatic loads (Balasch and Tort 2019), may enable, together with conceptualizations of stress and immune responses based upon evolutionary roadmaps (Becker et al. 2020; Taborsky et al. 2021), a precise framework to analyse probable outcomes of immune response in stressful environments.

It is expected that, confronted with human-induced abrupt changes, fish may rely on developmental plasticity mechanisms to cope with stressful environments (Petitjean et al. 2019), but to what extent altered phenotypes may influence survival and unexpected

changes in environmental variables is still unknown. An example may help to outline the difficulties of analysing a common stressor in the context of the fish immune response. Fish (with the exception of a few pelagic species with high metabolic basal rates) are ectothermic and their immune response diminishes in cold waters (Tong and Li 2020). Therefore, temperature changes are the main driver behind the evolution of immune repertories in fish, with pathogenic as an undesired direct effect of rising temperatures that strongly modulates host–pathogen interactions.

Any attempt to describe the effects of temperature on teleost immunity ends, as often happens with interspecies studies in fish, with a hard to summarize list of enhancements and impairments of temperature-regulated ups and downs of immune functionality. This is due to different experimental approaches, variable effects of optimal temperature-dependent virulence factors in pathogenic bacteria, several differences in the thermopreferendum of hosts and combined stressors (such as low oxygen levels, xenobiotics, emergent contaminants or hormone-mimicking pharmaceuticals) and the fact that temperature effects on teleost defensive responses are strongly seasonal, highly variable between species, populations with different life histories and even between individuals and sexes (Butler et al. 2013; Guijarro et al. 2015; Abram et al. 2017; Stewart et al. 2018; Marchand et al. 2019; Petitjean et al. 2020). Although no specific rules seem to apply to what is clearly a multifactorial sum of effects, recent surveys suggest that low temperatures may impair adaptive immune responses (especially T-cell-mediated immunity) and potentiate innate, unspecific defensive mechanisms, especially when several stressors are combined (Wentworth et al. 2018; Defo et al. 2019; Ignatz et al. 2020; Sun et al. 2020). In this sense, it has been suggested that infected or immunocompromised fish tend to actively search for hot spots to increase body temperature (Gräns et al. 2012; Boltaña et al. 2013). Inducing such behavioural fever (Covert and Reynolds 1977) contributes to enhance immune dynamics, mimicking the immune performance, both innate and adaptive, showed by temperate teleost species in spring (Buchtíková et al. 2011; Brown et al. 2016). Seasonal oscillations in temperature affect immunocompetence directly, by enhancing the circannual gene expression of immune-related genes (Gracey et al. 2004; Boltaña et al. 2013; Stewart et al. 2018; Abolfathi et al. 2020), but also indirectly, by interaction with the programmed onset of the reproductive hormonal axis, and seasonal cycles of pathogen abundance (Baekelandt et al. 2020). Long-term acclimation to non-optimal temperature regimes may improve an otherwise sluggish immune response at low temperatures, and accelerate phenotypic plasticity of immune-related gene expression responses, even in high-temperature scenarios (Scott and Johnston 2012; Abram et al. 2017; Tong and Li 2020).

To further complicate matters, the seasonality of immune function is multifactorial (Fig. 20.2), and the effects of temperature can be overridden by exogenous and endogenous variables, usually related to the onset of the reproductive hypothalamic–pituitary–gonadal (HPG) axis during the mating season, which affects immunocompetence. For example, male three-spine sticklebacks (*Gasterosteus aculeatus*) parasitized by *Schistocephalus solidus* and exposed to 17β-oestradiol (E2) suffered greater parasite load than females

(Macnab et al. 2016; Ling et al. 2020), indicating sex-specific (and also host-specific) effects on the interaction between the HPG and immune axis. Similarly, the effects of altered temperature regimes, combined with acute gill net entanglement and air exposure, two common stressors in aquaculture practices, suppressed female maturation and enhanced immune responses, increasing the parasite burden in a sex-dependent manner (Teffer et al. 2019). As mentioned before, shared receptors between immune and endocrine cells (Fig. 20.1), together with the intimate housing of the HPI and HPG axis in the teleost head kidney, facilitate neuroimmunoendocrine crosstalk, and estrogens have been deemed the culprit of immune modulations in fish (Szwejser et al. 2017; Cabas et al. 2018; Chaves-Pozo et al. 2018). The seasonal surges of E2 in teleost mature breeding females may affect immune responses, decreasing IgM levels and impairing cytokine networks (Cuesta et al. 2007; Seemann et al. 2016), altering the expression of Foxp3, a transcription factor for the development of T_{REG} cells (Wei et al. 2013). However, these and other immunosuppressive effects are markedly species-specific and still not well understood.

In addition, the link between temperature changes and pathogen distribution and virulence is expected to alter the immune plasticity of fishes (Claar and Wood 2020). In an ocean of microbes, temperature-driven pathogen outbreaks may act as an adaptive cue to boost metabolism, substitute behavioural fever for genuine endothermic fever, and abandon ectothermic metabolism in favour of a more efficient, memory-based, adaptive immunity, less dependent on low temperatures. In ectotherms, it has been argued that an immunity with increasingly cell consuming efficient affinity maturation of Ig in well-structured lymphoid organs cannot be realized due to an unaffordable metabolic cost by most ectotherms with slow metabolism (Lee 2006; Sandmeier and Tracy 2014). Besides, investing in increasingly efficient pathogen detectors may set the basis for an arm's race that selects for strategies of immune evasion and rapid changes in virulence from pathogens (Hedrick 2004; Guo et al. 2019), which would throw both host and pathogen to unending Red Queen evolutionary dynamics (Liow et al. 2011) of continuous adaptations simply to remain unharmed. These processes may have precluded an evolutionary urge for the development of fully functional endothermy in fish. Clearly, the origins of endothermy are far more complex and more species-specific than to be reduced only to immune solutions to compromised or stressful habitats (Nespolo et al. 2017; van de Pol et al. 2017), but the very few cases of functional endothermy found to date in fish (Soyano and Mushirobira 2018) seem to suggest that fish have adopted an immune strategy of resistance to pathogens, which appears somewhat defective compared with the mammalian-type hyper-specialized systems (such as immune receptor affinity maturation, multiple niche- and organ-specific cellular phenotypes, Ig isotype diversification and switching, and long-lasting memory). Between tolerance to pathogens (Råberg and Stjernman 2012), as showed by some aquatic invertebrates, or resistance, teleosts seem to have opted by fitting ectothermic metabolism to already highly plastic immune capabilities, suggesting that, in teleosts, the evolvability of the immune system has contributed to their evolutionary success, high diversity of lifestyles and widespread adaptive radiations (Solbakken et al. 2017).

Overall, even a common stressor of fish, namely temperature changes, requires an evolutionary background to delineate the foreground characteristics of stress-related immune performance. The consequences of the extreme diversity of fish lifecycles on stress-related immune function are overwhelmingly complex, but immensely rewarding for testing evolutionary models of immune system development coupled with ecological parameters. To date, few multiscale functional studies have addressed the intricacies of host–pathogen interaction in teleosts beyond the snapshot-like analysis of transcriptomes, proteomic surveys and metabolomic assessments of biological pathways. Genomic data are incredibly useful to systematize fish immune diversity and have rapidly becoming the by-default approach to evaluate environmental insults in fish physiology. However, integrated multiscale efforts are needed to discriminate between evolutionary changes in phenotypic plasticity in order to clarify the impact of combined stressors in host-pathogen immune negotiations in changing ecological contexts. Life story trade-offs often rest upon tortuous evolutionary paths across multiple interactions between overlapping species, competitive scenarios and unexpected environmental changes, sometimes ill-suited to human-induced extensive remodelling of contemporary environments. Combined analysis of environmental stressors in species-specific preferred niches may help to elucidate direct or indirect immune-related effects of environmental variables, which, to date, seem to affect immune responses in an indirect and elusive way. Ocean acidification, for example, seems to affect mainly acid–base homeostasis, branchial osmoregulation and overall metabolic scope, resulting in behavioural alterations, again in a species-specific manner (Esbaugh 2018). However, some results are controversial (Clark et al. 2020), and immune function under rising CO_2 partial pressures is poorly studied. Transcriptional analysis of acidification effects in gill tissues of barramundi (*Lates calcarifer*) suggests that acidified seawater modulates the expression of transcripts related to antigen processing and presentation, mucosal Ig and NK-mediated cytotoxicity (Ma et al. 2020). Similarly, Senegalese Sole (*Solea senegalensis*) enduring severe aquatic hypercapnia showed a short-term (up to 24 h) increase in plasma total bactericidal and antiprotease activities in mucosal lymphoid branchial tissues (Machado et al. 2020). However, chronic exposure (4 weeks) enhanced the expression of a limited repertoire of cytokine (IL-1β, IL-10) and cyclooxygenase 2 (COX2) transcripts related to inflammatory responses. Even if these results indicate an activated immune response in branchial tissues, the systemic effects of acidification are far from being resolved, and may be restricted mainly to local inflammation in gill mucosae or a result of impaired metabolic trade-offs that prime other physiological systems. In any case, as demonstrated by the evolutionary intricacies of amphibious fishes (Wright and Turko 2016), phenotypic and developmental plasticity must be included in the short- to long-term response to rapid environmental changes in aquatic CO_2 levels in fish. In this sense, resolving the fish immune tree of life will necessarily require a compilation of branching ecological influences on host lifetime, together with hologenomic approaches and niche-specific preferences.

20.6 Conclusion

Vertebrate immune systems suffer from acute horror vacui. Confronted with heavily microorganism-loaded environments, and constantly changing ornamental antigens anchored to pathogen surfaces, aquatic animals respond with functional redundancy of defensive components, multifunctional organs, constant production of unrequested naive lymphocytes and iterative cellular selection processes that completely fill the physiological tapestry of organisms. From an ecological perspective, fish immune phenotypes change over evolutionary time resembling developmentally and evolutionarily labile dose–response frameworks (Hedrick 2004; Grimholt 2018; Ravi and Venkatesh 2018). They are nurtured by the constant confrontation with stressors that question self-, non-self- and altered-self-antigenic components, but also by abrupt changes in environmental shelters, for instance, human-induced disturbances in preferred niches, or reproductive and metabolic adjustments to harsh habitats in the heart of a microbial-enriched environment (McCauley et al. 2015; Kelly and Salinas 2017; Ling et al. 2020). Fish possess the unspecific immune response to foreign molecules characteristic of invertebrates, reinforced by the canonical adaptive, specific and energetically expensive inflammatory reactivity of vertebrates (Palti 2011; Flajnik 2018; Patel et al. 2018; Rebl and Goldammer 2018). However, as discussed, a handful of exclusive characteristics and drawbacks differentiate fish immunity from that found in endothermic (i.e. birds and mammals) vertebrates. Several factors account for these differences, the most preeminent being the (1) physical, microbiological and human-influenced characteristics of aquatic dwellings, (2) long-vanished palaeoclimatic events (Solbakken et al. 2017) and (3) the high species specificity of immune responses, partly ameliorated by phenotypic and developmental plasticity to environmental changes (Farrell and Franklin 2016).

Overall, the immune reactivity of fish to environmental insults is influenced by the type and intensity of exogenous stressors (alone or combined), may be modulated by the phenotypic plasticity of behavioural responses, depends on sex-, population- species-specific and niche-related differences, and suffers the lags in the maturation of adaptive immunocompetence in larvae and adults. Even though stress-related neuroendocrine interactions have been and continue to be thoroughly analysed in teleosts, and several studies addressed neuroimmunoendocrine influences in stressed fish (Verburg-van Kemenade et al. 2017; Das et al. 2018; Shepherd et al. 2018; Hou et al. 2019), the impact and crosstalk of immune altered states in the activation of stress-related neurohormonal frameworks are still not fully characterized in fish. This is partly due to the model-centric methodological approach that favours some laboratory-friendly, novel translational research-related or simply commercial teleost species, at the expense of less known but more abundant and diversified fish (Schartl 2014). In an attempt to describe a more global picture of allostatic load effects in stressed fish, the focus now is on multibiomarker approaches that may render accurate descriptions of fish immunoreactivy in realistic multifactorial scenarios, where several combined parameters (temperature, pathogen load, multiplicity of stressors, behavioural phenotypes, etc.) can be analysed

simultaneously in an integrated framework (Khansari et al. 2018; Silva et al. 2018; Vargas et al. 2018; Dallarés et al. 2020). Unfortunately, we are still far from the development of an analytical framework, such as *stressotopes* (Balasch and Tort 2019) that may allow for the comprehensive multilevel description of evolved adaptive interactions between an individual's physiology and their preferred niche. However, a promising step may be the hologenomic approach (Limborg et al. 2018), in which the diverse methodologies for the expression analysis of fish host genomes, together with commensal and pathogenic mucosal microbiota, coalesce to integrate molecular and functional data in the light of evolutionary choices under environmental pressures.

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