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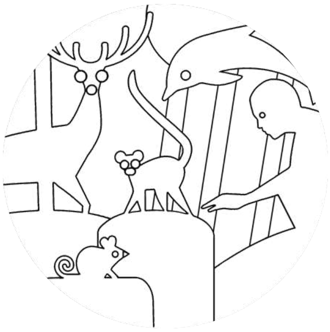
Cartilaginous vs Bony Fish: Evolutionary Perspectives on Stress and Immune Adaptations



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INDEX

SUMMARY

The present thesis provides a comparative review of the immune system organization and stress physiology of cartilaginous fish (Chondrichthyes) and bony fish (Osteichthyes), examining how their immune and stress responses have shaped their adaptation and survival in the marine environment. Both groups share the basic architecture of vertebrate adaptive immunity, immunoglobulins, T cell receptors, and major histocompatibility complex (MHC) molecules, that have been inherited from the common jawed vertebrate ancestor from approximately 450 million years ago; yet, they have evolved notably distinct immune strategies over the course of their independent evolutionary histories.

Cartilaginous fish have several features that are unique among vertebrates, including the single immunoglobulin new antigen receptors (IgNAR), a heavy chain only single domain antibody, the new antigen receptor T cell receptors (NARTCR), somatic hypermutation at T cell receptor loci, and the Leydig and epigonal organs as exclusive hematopoietic sites. Their stress response is mediated by 1α-hydroxycorticosterone rather than cortisol and their K-selected reproductive strategy, makes them vulnerable to physiological consequences of chronic anthropogenic stress. Teleost bony fish, the focus of the bony fish discussion in this thesis, as the most extensively studied subgroup of Osteichthyes, possess a structurally detailed mucosal immune system, with all three complement pathways and a characterized cortisol-mediated hypothalamic pituitary interrenal (HPI) axis that has well-documented immunosuppressive effects under chronic stress.

Comparative analysis helps understand neither group possess a superior immune system, instead, each portray a logical evolutionary solution to the challenge of surviving in an aquatic environment under the conditions of increasing anthropogenic pressure. Understanding the physiological adaptations of both cartilaginous and bony fish is directly relevant to marine animal health, conservation biology, and biomedical research. This review aims to contribute to that understanding and emphasize the areas in which further research is needed.

1. INTRODUCTION

The accelerated rate of the global environmental change has rendered the conservation of marine species a matter of increasing scientific concern. Constant anthropogenic activity such as chemical pollution, rising water temperatures, habitat destruction, and commercial fish captures, exposes marine organisms to physiological stressors that can jeopardize their immune and reproductive systems, ultimately threatening population survival (Skomal & Mandelman, 2012; Wheeler et al., 2020). Understanding the immune system functions, stress tolerance, and the fish adaptability to the challenges they face, is a priority for developing evidence-based animal health and welfare strategies, as well as to design conservation measures that are based on the biology of the species researchers seek to protect.

Among marine vertebrates, fish represent an extremely diverse and ecologically important group. Occupying almost every aquatic habitat in the world, they serve as keystone species in marine food webs and provide essential ecological services whose disruption carries consequences that extend beyond the individual populations. Within this group, two major classes are differentiated by their evolutionary importance and the scientific interest in their immune systems. The cartilaginous fish, class Chondrichthyes, including sharks, skates, and rays; and the bony fish, class Osteichthyes, specifically teleosts which account for the majority of the living fish species. The class Osteichthyes includes three major subgroups: the teleosts, the lungfish, and the coelacanths. However, as the available immunological and stress physiology research overwhelmingly concern to teleosts, demonstrating both their extraordinary species diversity and the ecological and economic significance, the present thesis focuses primarily on this subgroup as the representative group of bony fish. The two groups belong to the Gnathostomata, the jawed vertebrates, and represent the most phylogenetically distant group from mammals known to possess an adaptive immune system founded upon immunoglobulins, T cell receptors, and the major histocompatibility complex (MHC) molecules (Smith et al., 2019). A fundamental difference between the two groups lies in their skeletons, bony fish have a calcified bone skeleton while cartilaginous fish have a skeleton entirely of cartilage; a distinction with direct implications for immune cell production, considering the absence of bone marrow in cartilaginous fish and their accompanying dependency on alternative hematopoietic organs (Smith et al., 2019; Walsh et al., 2006).

The two lineages diverged from a common ancestor approximately 450 million years ago, at which point they commenced their independent evolutionary trajectories that have produced notably different, yet equally impressive immune strategies (Smith et al., 2019). Cartilaginous fish are the oldest extant vertebrates to possess an immunoglobulin based adaptive immune system, meaning they are invaluable points of reference for understanding how the vertebrate immunity first evolved and how it has been modified, refined, or conserved over time (Mitchell & Criscitiello, 2020). Bony fish represent one of the most diverse vertebrate groups, having undergone extraordinary ecological radiation, and have developed an elaborate immune architecture including a dedicated mucosal immunoglobulin class and four mucosal lymphoid tissue compartments reflecting the demands placed upon a group that inhabit all types of aquatic environments on Earth (Salinas, 2015; Smith et al., 2019).

Understanding the immune systems and stress physiology of these two groups is essential to comprehend how vertebrate survival and adaptability function at a physiological level. The bony fish stress response is mediated through the hypothalamic pituitary interrenal (HPI) axis which drives the release of cortisol, a glucocorticoid hormone that mobilizes energy reserves but suppresses the immune system function under conditions of chronic elevation (Wendelaar Bonga, 1997). In cartilaginous fish, the functionally equivalent stress hormone is 1α-hydroxycorticosterone (1α-OHB), which is a corticosteroid that is unique to chondrichthyans whose glucocorticoid activity has only recently been confirmed (Anderson, 2012; Ruiz-Jarabo et al., 2019). The relationship between chronic stress and immune function is therefore a central concern in this field. Sustained stress directly compromises the immune system of the two groups, decreasing disease resistance, impairing reproductive physiology, particularly in species with slower life histories, carrying population level consequences that go beyond the individual organism (Wheeler et al., 2020; Yada & Tort, 2016).

Cartilaginous fish are particularly notable in this regard, with several features of their biology attracting scientific attention beyond the conservation context. Their immunoglobulin new antigen receptors (IgNAR), a heavy chain only single domain antibody, is capable of binding epitopes that are normally inaccessible to conventional antibodies and has consequently gained the attention of scientists in the biomedical and pharmaceutical field for research, as a platform for therapeutic antibody development (Criscitiello, 2014). Their K-selected reproductive strategies, characterized by their late sexual maturity, small litter sizes, and long gestation periods, makes them among the most conservation sensitive vertebrates in the world, making the interactions between chronic anthropogenic stress, reproductive failure, and immune suppression a matter of scientific and conservation urgency for these fish (Carrier et al., 2010; Skomal & Mandelman, 2012).

1.2 Aim

The present thesis aims to provide a comparative review of the immune systems and stress physiology of cartilaginous (Chondrichthyes) and bony fish (Osteichthyes), examining how approximately 450 million years of independent evolutionary divergence has shaped two distinct yet equally functional immune strategies. Specifically, this work sets out to illustrate and compare the molecular and structural organization of the innate and adaptive immune systems of the two groups; to analyze how the stress response is mediated by cortisol predominantly in teleost bony fish through the HPI axis, and by 1α-OHB in cartilaginous fish, modulates immune function and reproductive physiology under the conditions of chronic anthropogenic stress; and to evaluate the conservation implications of these physiological differences, with particular attention to the population level vulnerability of cartilaginous fish considering their K-selected reproductive strategy. Through a critical review of the available scientific literature, this thesis aims to contribute to the field of comparative immunology and to identify the areas in which further research is critically required, specifically regarding the elasmobranch stress response and the relationship with immunosuppression and reproductive failure. It is hoped that a deeper understanding of these systems will contribute to the comparative immunology as a discipline and to protect and manage two of the most scientifically and ecologically important groups of animals in the oceans of our world.

2. FISH IMMUNOLOGY

2.1 Innate and Adaptive Immunity; The Organization, Cells, and Molecules

Jawed vertebrates have an immune system consisting of two distinct however interacting branches, the innate and adaptive immune systems. These two responses provide protection against foreign pathogens and cellular damage within a living organism. While the organization of these systems is consistent across vertebrates, fish represent the earliest jawed vertebrates, the Gnathostomata, known to retain both forms of protection that is now substantial among higher vertebrates, making them a crucial point of reference to understand the evolution of the vertebrate immunity (Smith et al., 2019).

The innate immune system is the first line of defense against infection, responding swiftly and non-specifically to the foreign pathogens, without distinguishing between the antigens and retaining immunological memory. There are three different factors that make up its mechanisms: physical barriers, humoral response and the cellular components. Physical barriers such as the skin, epithelial lining, and mucus membranes, act as an initial block, preventing the pathogen from entering (Secombes & Wang, 2012). When the barriers are breached, there is the activation of the cellular and humoral mechanisms. There is pathogen associated molecular patterns (PAMPs) that are expressed after the invasion, that are recognized by pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs) (Magnadòttir, 2006). These TLRs bind, initiating a downstream signaling that produces cytokines and chemokines, that recruit immune cells and activate leukocytes (Smith et al., 2019).

Macrophages and neutrophils are fundamental components of innate immunity. Macrophages destroy pathogens through phagocytosis ingesting the foreign pathogen; secreting pro-inflammatory mediators such as cytokines, lipids, and amines to enhance and regulate inflammatory reactions; and fulfilling the role of antigen presenting cells (Secombes & Wang, 2012). Regarding neutrophils, they release antimicrobial enzymes side by side with phagocytosis to quickly contain the infection and prevent further spread (Smith et al., 2019). The humoral response consists of a complement system, a cascade of proteins activated through three different pathways, classical, alternative and lectin pathways. The classical is triggered by antibody antigen complexes, while the alternative through pathogen surface components, and the lectin pathway by mannose binding lectin that binds to the surface sugars (Nonaka & Smith, 2000). These pathways converge on the cleavage of complement component C3, a central protein of the complement system; producing C3a which promotes inflammation and C3b that marks pathogens for their destruction through phagocytosis. This leads to the formation of the membrane attack complex (MAC) that causes pathogen lysis (Magnadòttir, 2006; Smith et al., 2019).

When the innate mechanisms are inadequate, adaptive immunity activates following several days of exposure to the foreign organism. Adaptive immunity is defined by having a slower response time, its ability to target specific antigens, and immunological memory (Secombes & Wang, 2012). The major histocompatibility complex (MHC) molecules have pathogen derived peptides that are presented by dendritic cells to T lymphocytes in lymphoid tissue (Smith et al., 2019). There is cell mediated immunity, with the two cell types CD4+ helper T cells and CD8+ cytotoxic T cells. The helper T cells help to coordinate an immune response by cytokine secretion while the cytotoxic T cells, destroy any cells that are infected or atypical through apoptosis, a programmed cell death (Buchmann & Secombes, 2022). This process increases the memory T cells once the infection has been overcome, allowing future recognition of the infection and faster response if it were to repeat itself. Then there is humoral immunity, in which B lymphocytes produce immunoglobulins that neutralize pathogens, promote phagocytosis and activate the complement system. When the infection is recognized, B cells are activated, cloned and differentiate into plasma cells which cause antibodies to be released and memory B cells which memorize these pathogens to quicken the response for future encounters.

2.2 General Immune System Structure of Bony and Cartilaginous Fish

Both cartilaginous fish (Chondrichthyes) and bony fish (Osteichthyes) possess innate and adaptive immune systems, as they have branched from a common ancestor approximately 450 million years ago (Smith et al., 2019). Both groups have the first lines of defense, the physical barriers of the skin, gills, and gastrointestinal tract. Their skin secretes mucus which contains lysozymes, antimicrobial peptides, lectins, and complement proteins that are able to nullify pathogens at the surface. However, the gill structure differs; in cartilaginous fish, the gills are supported along almost their entire length by an interbranchial septum with the presence of external branchial slits, while bony fish have the interbranchial septum greatly reduced with the gills opening through a single opercular covering (Smith et al., 2019).

Chondrichthyes and Osteichthyes, maintain networks of immune cells that are ingrained within the tissue, known as gut, associated lymphoid tissue (GALT) and gill associated lymphoid tissue (GIALT). This helps them protect their mucosal surface which are exposed on the gut and gills. GALT and GIALT contain myeloid and lymphoid cells that are spread across the mucosal lining to allow constant local surveillance at the locations of possible pathogen entry (Salinas, 2015; Smith et al., 2019). Teleost bony fish also maintain the immune cell population in the skin and nasopharyngeal mucosa, also known as the skin, associated lymphoid tissue (SALT) and nasopharynx associated lymphoid tissue (NALT); together making up the mucosal associated lymphoid tissue (MALT) system. These same structures have not been found to be present in cartilaginous fish (Salinas, 2015; Yu et al., 2020).

In bony fish, leukocyte production occurs primarily in the anterior kidney, like the functional equivalent of mammalian bone marrow, and the thymus. In cartilaginous fish, however, these sites are the epigonal organ (associated with the gonads), the Leydig organ (associated with the esophagus), thymus, and the spleen (Smith et al., 2019). Both groups share the innate immune cell types macrophages, neutrophils, and granulocytes, but the distribution and classification of them differs between species.

A notable difference between the two groups are the pathways of the complement system present in the innate humoral immunity. Both have the classical and alternative pathways but, the lectin pathway is absent or perhaps non-functional in cartilaginous fish. The genes encoding mannose binding lectin (MBL), ficolin, and the associated serine protease MASP2, all the essentials of lectin pathway activation, have failed to be found in any cartilaginous fish studies to date. By contrast, bony fish possess all three complement pathways in a form broadly comparable to that of mammals (Nonaka & Smith, 2000; Smith et al., 2019).

2.3 Differing and Shared Traits

Both cartilaginous and bony fish share the fundamental components of vertebrate adaptive immunity: immunoglobulins, T cell receptors, and MHC molecules. IgM is the most ancient immunoglobulin class, present across all jawed vertebrates and found in both groups, promoting phagocytosis, antibody-dependent cytotoxicity, and complement activation. Both groups also possess immunological memory; however, their adaptive immune response is considerably slower than that of mammals, requiring approximately three to four weeks before specific antibody concentrations reach detectable levels in the blood (Smith et al., 2019).

Beyond IgM, the immunoglobulin repertoires of the two groups diverge completely. Teleost bony fish possess IgM, IgD, and IgT, the latter being specific to teleosts and functionally analogous to mammalian IgA in its role in mucosal immunity. Studies have demonstrated that during parasitic infection, IgT-positive B cells increase markedly in the intestinal mucosa while IgM-positive B cells remain unchanged, confirming a distinct mucosal role for IgT (Salinas, 2015; Smith et al., 2019). Cartilaginous fish, by contrast, possess IgM, IgW, and the immunoglobulin new antigen receptor (IgNAR), the latter being exclusive to this group and capable of binding antigens independently without the light-chain support required by conventional antibodies (Dooley & Flajnik, 2006). The genomic organisation of immunoglobulin heavy chain genes also differs, as cartilaginous fish employ a cluster arrangement, with each cluster containing its own complete set of V, D, J, and C gene segments, while teleost bony fish use a translocon arrangement more similar to that of mammals (Smith et al., 2019).

Both cartilaginous and bony fish produce T cells in the thymus; however, cartilaginous fish are unique in possessing the new antigen receptor T cell receptor (NARTCR), a variant of the TCR-delta that incorporates an additional variable domain structurally related to the VNAR domain of IgNAR, a feature absent in all other vertebrates (Criscitiello, 2014; Smith et al., 2019). Furthermore, cartilaginous fish are the only vertebrates known to employ somatic hypermutation (SHM), a process in which mutations are introduced into receptor genes to enhance pathogen recognition, at the T cell receptor loci. In all other vertebrates, this process is restricted to antibody genes in B cells alone (Criscitiello, 2014). Finally, the organisation of MHC molecule-encoding genes, which produce the proteins responsible for presenting pathogens to T cells, differs between the two groups: in cartilaginous fish, MHC class I and class II genes are located on the same chromosome, whereas in teleost bony fish they are distributed across different chromosomes (Smith et al., 2019; Veríssimo et al., 2023). The main shared and differing immune system features between cartilaginous and bony fish are summarized in Table 1, presented at the conclusion of Section 4.

3. IMMUNE SYSTEM OF CARTILAGINOUS FISH

3.1 The Unique Organs of Cartilaginous Fish

There are several primary lymphoid organs that are uniquely found in cartilaginous fish. Hematopoiesis, the process by which all blood and immune cells are produced and continuously replenished, takes place in the bone marrow and thymus of bony fish and mammals. Cartilaginous fish, however, have a skeleton completely composed of cartilage and therefore lack bone marrow entirely. Instead, the epigonal organ and the Leydig organ fulfil the same hematopoietic role for cartilaginous fish as bone marrow does for bony fish (Mitchell & Criscitiello, 2020; Walsh et al., 2006).

The epigonal organ is a lymphomyeloid tissue closely associated with the gonad, and the Leydig organ is found along the esophagus (Walsh et al., 2006). Both organs have been identified as sites of active lymphocyte development, in which the recombination activating genes (RAG) and the terminal deoxynucleotidyl transferase (TdT) are present, both essential for generating a diverse antigen receptor repertoire during lymphocyte maturation (Walsh et al., 2006). Both organs have been confirmed to provide hematopoiesis comparably to higher vertebrates; Mitchell and Criscitiello (2020) describe them as analogous to mammalian bone marrow, while Walsh et al. (2006) regard them as functional equivalents. In their review of elasmobranch immunity, Luer, Walsh, and Bodine, as cited in Carrier et al. (2010), identified the Leydig organ and epigonal organ as the principal hematopoietic feature distinguishing cartilaginous fish from all other jawed vertebrates. In addition to these two organs, cartilaginous fish also possess the spleen as a secondary lymphoid organ facilitating immune activation, and the thymus, which is responsible for T lymphocyte maturation (Carrier et al., 2010; Smith et al., 2019).

The adaptive immunity of cartilaginous fish operates more slowly than that of teleost bony fish or mammalian adaptive immunity. Following exposure to a foreign antigen, specific IgM antibody responses can take from weeks to months to mature, and antibody levels can persist long after resolution of infection. Studies conducted on nurse sharks (Ginglymostoma cirratum) have demonstrated that antibody levels persisted at elevated concentrations for up to 28 months following resolution of infection (Smith et al., 2019). Over the course of the immune response, IgM antibodies progressively increase in binding affinity through affinity maturation, transitioning from an initial low-affinity response to a more refined and highly specific antibody production. This characteristically slow adaptive response reflects the evolutionary distinctiveness of the Chondrichthyan immune system, whilst demonstrating that its fundamental functionality is conserved with that of bony fish.

3.2 Immune Mechanisms Unique to Cartilaginous Fish

Immunoglobulin Reserve: IgM, IgW, and IgNAR

The immunoglobulin repertoire of cartilaginous fish differs from that of bony fish and other jawed vertebrates. Teleost bony fish possess IgM, IgD, and IgT, while cartilaginous fish possess IgM, IgW, and the immunoglobulin new antigen receptor (IgNAR) (Carrier et al., 2010; Dooley & Flajnik, 2006; Smith et al., 2019). IgM is the most ancient immunoglobulin class, present across all jawed vertebrates. In cartilaginous fish, IgM is found in both monomeric and pentameric forms and contributes to both systemic and mucosal defence (Smith et al., 2019). IgW shares a common evolutionary ancestor with the mammalian IgD, and its presence in cartilaginous fish, coelacanths, and lungfish has supported the proposal that IgD and IgW represent one of the most evolutionarily conserved immunoglobulin lineages in vertebrate history (Dooley & Flajnik, 2006).

The most structurally distinctive immunoglobulin is the IgNAR, in which the designation NAR refers to new antigen receptor, reflecting its unique structural properties. IgNAR is composed of a homodimer of two heavy chains with no light chain association (Smith et al., 2019). It is an antigen receptor first identified in the nurse shark (Ginglymostoma cirratum), in which each heavy chain contains a variable domain known as the VNAR domain, capable of binding antigens independently without requiring light chain support (Criscitiello, 2014; Smith et al., 2019). The VNAR domain permits access to specific binding sites on antigens that are normally inaccessible to conventional antibodies, including enzyme active sites and deep receptor clefts (Criscitiello, 2014). As noted by Carrier et al. (2010), this distinctive structural feature of elasmobranch immunoglobulins provides unique insight into the evolution of antibody architecture that cannot be obtained from mammalian models alone.

The genomic organisation of immunoglobulin heavy chain genes also differs between the two groups. In cartilaginous fish, a cluster arrangement is employed for the V, D, J, and C gene segments, with recombination occurring independently within each cluster rather than across segments. Teleost bony fish, by contrast, use a translocon arrangement more similar to that of mammals, in which V, D, J, and C segments are arranged along a single array, permitting recombination across segments in multiple combinations and thereby generating considerably greater antibody diversity. A particularly distinctive feature of the cartilaginous fish cluster arrangement is the phenomenon of germline joining, whereby certain antibody configurations are pre-encoded in the genome from birth, representing a unique mechanism of immune preparedness that has not been observed in other vertebrates (Smith et al., 2019).

The NARTCR and Somatic Hypermutation

Cartilaginous fish also possess a variant of the T cell receptor known as the new antigen receptor T cell receptor (NARTCR), as previously defined in Section 2.3. This receptor is a variant of the TCR-delta that incorporates an additional variable domain structurally related to the VNAR domain of IgNAR, a feature absent in all other vertebrates (Criscitiello, 2014; Smith et al., 2019).

In addition, cartilaginous fish are unique in their capacity to diversify T cell receptors through somatic hypermutation (SHM), a process in which mutations are introduced into receptor genes to enhance the precision of pathogen recognition. In all other vertebrates, this process is restricted to antibody genes in B cells. In cartilaginous fish, however, this ability extends to T cell receptor genes, providing an additional layer of receptor diversification. This was first demonstrated in sandbar sharks (Carcharhinus plumbeus), in which both the TCR-gamma and TCR-alpha loci were found to undergo somatic hypermutation (Criscitiello, 2014). Although initially considered entirely unique to this lineage, it has since been suggested that this capacity may not be exclusively confined to cartilaginous fish; however, it remains exceptionally rare among vertebrates and continues to exemplify the extraordinary nature of lymphocyte diversification in this group.

3.3 Disease Susceptibility and Response to Infection

A common misconception regarding cartilaginous fish is that they are entirely resistant to disease, including cancer. This has been decisively contradicted by the scientific literature. A retrospective study of 1,546 elasmobranch specimens across at least 60 species identified bacterial infections in approximately 15% of the studied population, parasitic infections in approximately 9%, and both benign and malignant tumor formation in six documented cases (Garner, 2013). Infectious agents identified included nematodes, trematodes, ciliates, and bacterial pathogens responsible for dermatitis, bronchitis, and sepsis, with additional cases of fungal infection, cardiovascular disease, and toxin-associated pathology also recorded. It must be acknowledged that Garner (2013) relied predominantly on samples submitted to a diagnostic laboratory from captive or clinically abnormal individuals rather than directly from wild populations, introducing the possibility of submission bias. Nevertheless, the findings clearly demonstrate that cartilaginous fish are susceptible to infectious disease and are not immunologically invulnerable, a point that is important for grounding the comparative analysis presented in subsequent sections.

3.4 Stress Response, Reproductive Physiology, and Conservation Repercussions

1α-hydroxycorticosterone: The Cartilaginous Fish Stress Hormone

One of the most physiologically distinctive features of cartilaginous fish in comparison to bony fish is their primary corticosteroid stress hormone. In teleost bony fish, the dominant glucocorticoid released in response to stress is cortisol, produced by the interrenal tissue and regulated through the hypothalamic-pituitary-interrenal (HPI) axis. In cartilaginous fish, the functionally equivalent hormone is 1α-hydroxycorticosterone (1α-OHB), a corticosteroid unique to chondrichthyans (Anderson, 2012; Carrier et al., 2010). The synthesis of 1α-OHB is stimulated by adrenocorticotropic hormone (ACTH) from the pituitary, consistent with regulation through an HPI-equivalent axis (Ruiz-Jarabo et al., 2019).

For many years, the precise functions of 1α-OHB remained poorly characterised. Anderson (2012) highlighted that studies investigating its glucocorticoid and mineralocorticoid actions were scarce at the time of their review. Ruiz-Jarabo et al. (2019) were the first to provide direct evidence of glucocorticoid activity by 1α-OHB in elasmobranchs, demonstrating that plasma 1α-OHB concentrations increased markedly following acute stress in catsharks (Scyliorhinus canicula), accompanied by elevated plasma glucose concentrations consistent with glucocorticoid-mediated energy mobilisation. These findings confirm 1α-OHB as functionally analogous to cortisol in teleosts.

Stress, Immune Suppression, and the Relationship with Neuroendocrine Signaling

A well-established connection exists between stress and immune function in vertebrates, operating through a network of hormonal and neuroendocrine interactions. Yada and Tort (2016) demonstrated that stressors activate corticosteroid and catecholamine systems which, through receptor-mediated signalling, interact directly with immune cells and reduce their capacity to respond to pathogens. Whilst acute stress may transiently enhance certain innate immune parameters as the organism mounts an immediate physiological response, the authors established that chronic or sustained stress leads to progressive immunosuppression, causing disease resistance to decline, pathogen susceptibility to increase, and allostatic load to accumulate within the organism. Yada and Tort (2016) further demonstrated that under conditions of sustained stress, energy and physiological resources are redirected away from immune function, reproduction, and growth, as the organism prioritises immediate survival. Although the framework established by Yada and Tort (2016) focused primarily on teleost fish and cortisol-based stress physiology, the principle that sustained corticosteroid elevation impairs immune function provides a valid basis for interpreting the elasmobranch stress response. In cartilaginous fish, 1α-OHB fulfils the glucocorticoid role, and the physiological consequences of prolonged stress would be expected to follow broadly similar pathways, although direct evidence for this relationship in elasmobranchs remains limited (Anderson, 2012; Skomal & Mandelman, 2012).

Acute and Chronic Stress: Physiological Consequences

The physiological stress responses of marine elasmobranchs exposed to anthropogenic stressors have been characterized in a foundational review by Skomal and Mandelman (2012). Although published over a decade ago, this review remains the most comprehensive synthesis of elasmobranch stress physiology available and continues to be widely cited in the field. Their review documented the primary stress response, defined as the immediate neuroendocrine reaction involving the rapid release of catecholamines and corticosteroids; and the secondary stress response, defined as the subsequent physiological and hematological changes including hyperglycemia, ionic disruption, and alterations in blood chemistry. These responses were found to be broadly comparable to those of teleost fish, with the principal distinction being that 1α-OHB serves as the hormonal mediator in place of cortisol, and that the rate of physiological recovery varies considerably depending on the species and the nature of the stressor. Critically, Skomal and Mandelman (2012) identified a complete absence of studies investigating the tertiary stress response in elasmobranchs at the time of their review, representing a significant gap in the literature that continues to require attention.

Stress and Reproductive Health

Research has since begun to address this gap. Wheeler et al. (2020) reviewed evidence regarding the effects of anthropogenic stress on elasmobranch development and reproduction, documenting that stress arising from captures can induce premature parturition in gravid females, either during or following the capture event itself. In teleost fish, elevated glucocorticoids suppress gonadotropin release, interfering with gonadal steroidogenesis and reducing both reproductive hormone production and gamete quality. Whilst direct hormonal evidence for the same mechanistic pathway in elasmobranchs remains limited, the documented occurrence of stress-induced premature parturition and reproductive disruption in cartilaginous fish is consistent with this broader physiological framework (Wheeler et al., 2020).

The conservation implications of stress-induced reproductive damage in cartilaginous fish are considerable. Elasmobranchs are characterised by late sexual maturity, small litter sizes, and gestation periods ranging from several months to over a year. Population recovery following decline is therefore substantially slower than in bony fish, particularly given that many elasmobranch populations are already under pressure from overfishing and habitat degradation. Any anthropogenic stressor capable of reducing reproductive success, whether through pollution, fishing pressure, or habitat destruction, carries disproportionate consequences for population viability (Skomal & Mandelman, 2012; Wheeler et al., 2020). The interplay between stress physiology, immune function, and reproductive biology therefore underscores the critical importance of advancing research on the Chondrichthyan stress response, not only for the field of comparative immunology, but for the long-term conservation of this group.

4. IMMUNE SYSTEM OF BONY FISH

4.1 The Primary Lymphoid Organs of Bony Fish

Bony fish belong to the class Osteichthyes, more specifically, the ray-finned teleosts, which represent the largest and most diverse group of vertebrates, with over 30,000 species living in almost every aquatic environment on Earth (Wendelaar Bonga, 1997). Despite their diversity, the teleost immune system is well conserved across the group of fish, sharing considerable structural homology with the immune systems of higher vertebrates, such as mammals, all while maintaining features that represent both the necessities of an aquatic lifestyle and the evolutionary history of their ancestors (Smith et al., 2019).

As with all jawed vertebrates, bony fish have both the innate and adaptive immune systems. The innate system provides the first line of defence through physical barriers such as the skin, scales, and mucus membranes; through cellular mechanisms including macrophages, neutrophils, and natural killer-like cells; and through humoral components such as lysozymes, antimicrobial peptides (AMP), and complement proteins (Secombes & Wang, 2012). The production of immune cells, a process known as haematopoiesis, occurs in the anterior kidney, also known as the head kidney, which fulfils a role similar to that of bone marrow in mammals. The thymus is the site of T lymphocyte maturation, while the spleen and gut-associated lymphoid tissue (GALT) function as the secondary lymphoid organs where the immune response is initiated and expanded (Smith et al., 2019).

The development of the lymphoid organs follows a maintained pattern within the teleost species. The anterior kidney is established early in development and remains the primary site of leukocyte production throughout the organism's life, continuously generating myeloid and lymphoid cells that populate both the innate and adaptive immune compartments (Secombes & Wang, 2012). The thymus, which develops from pharyngeal pouches during the early larval stages, is responsible for the maturation and selection of T lymphocytes and is mostly active in juvenile fish, although it is preserved throughout adulthood in many species (Smith et al., 2019). The spleen develops as the primary secondary lymphoid organ, as the major site of antigen presentation and adaptive immune activation, and the GALT matures concurrently with the gastrointestinal tract, becoming an important site for mucosal immune monitoring (Secombes & Wang, 2012; Smith et al., 2019). Together with the mucosal-associated lymphoid tissue (MALT) system, which includes the GALT, gill-associated lymphoid tissue (GIALT), skin-associated lymphoid tissue (SALT), and nasopharynx-associated lymphoid tissue (NALT), these tissues generate and maintain the teleost immune supply across all body surfaces (Salinas, 2015; Smith et al., 2019).

The immunoglobulin repertoire is generated through V(D)J recombination, a somatic process by which variable (V), diversity (D), and joining (J) gene segments are randomly organized in the anterior kidney in order to produce a highly diverse array of B cell receptors and secreted antibodies, providing the molecular basis for the antigen specificity of the adaptive immune response (Smith et al., 2019).

4.2 Immune Mechanisms of Bony Fish

Immunoglobulin Repertoire: IgM, IgD, and IgT

The adaptive immune system of teleost bony fish is similar to the mammalian response, with B lymphocytes producing immunoglobulins, T cell receptors expressed on T lymphocytes, and MHC molecules presenting pathogen-derived peptides to T cells (Smith et al., 2019). However, there are distinguishing features that differentiate the teleost immune system from that of mammals. Teleost bony fish possess three principal immunoglobulin classes: IgM, which is the most common and dominant; IgD, which is present in both teleosts and mammals but is less functionally characterised in teleosts; and IgT, also referred to as IgZ in some species, which is specific to teleosts and functionally analogous to mammalian IgA in its role in mucosal immunity (Salinas, 2015; Smith et al., 2019). IgT-positive B cells increase markedly in mucosal tissues such as the intestine during parasitic infection, whilst IgM-positive B cells remain unchanged, confirming that IgT fulfils a distinct and specialised role in mucosal defence (Salinas, 2015; Smith et al., 2019).

The MALT System and Mucosal Defence

The MALT system of teleost bony fish is considerably more structurally developed than that of cartilaginous fish, comprising the GALT, GIALT, SALT, and NALT (Yu et al., 2020). These mucosal sites represent the primary points of first contact with waterborne pathogens and together constitute an important line of defence for the immune system. The adaptive immunity of teleosts is functional and capable of generating immunological memory; however, it produces a slower and generally weaker response than that of mammals. A specific antibody response following pathogen exposure can take up to four weeks to reach detectable levels in the blood, and the process of affinity maturation, by which antibody binding affinity is enhanced over time, is also less efficient than in mammals (Smith et al., 2019).

Comparison with Cartilaginous Fish

In comparison to cartilaginous fish, bony fish possess both greater structural complexity in the mucosal immune system and a more complete complement pathway repertoire. As established in Section 2, cartilaginous fish lack the genes encoding mannose-binding lectin (MBL), ficolin, and the serine protease MASP2, indicating that the lectin pathway is either absent or non-functional, whilst teleosts possess all three complement pathways (Nonaka & Smith, 2000; Smith et al., 2019). Teleosts also possess IgT, specific to mucosal immunity, for which no confirmed equivalent has been identified in cartilaginous fish, whose mucosal tissue is less structurally elaborate (Salinas, 2015; Smith et al., 2019). Cartilaginous fish, by contrast, possess the IgNAR single-domain antibody, the NARTCR, somatic hypermutation at the T cell receptor loci, and the Leydig and epigonal organs as exclusive haematopoietic sites. Each group has evolved a distinct but equally intricate means of immune protection, shaped over 450 million years of independent evolution (Smith et al., 2019).

4.3 Disease Susceptibility and Response to Infection

Teleost bony fish are susceptible to a wide range of infectious diseases, including bacterial, viral, parasitic, and fungal infections. Their disease resistance is closely linked to the integrity of the mucosal immune system and the speed and magnitude of the IgM and IgT antibody response following pathogen entry. The MALT system provides layered protection across all major body surfaces, and the compartmentalisation of IgT to mucosal sites during infection demonstrates a specific and well-adapted immune response to the diverse pathogen pressures associated with inhabiting every type of aquatic environment (Salinas, 2015; Smith et al., 2019). The teleost adaptive immune response, whilst functional and capable of developing immunological memory, is considerably slower and less potent than that of mammals, meaning that innate immune mechanisms and mucosal defences serve as the primary barrier against infection, with the adaptive response providing an essential secondary layer of protection (Smith et al., 2019).

4.4 Stress Response, Reproductive Physiology, and Conservation Repercussions

The Stress Response System in Bony Fish

There are two principal hormonal axes that constitute the physiological stress response in bony fish, both well characterised and conserved among vertebrates. The first is the brain sympathetic chromaffin cell axis, analogous to the mammalian sympathetic adrenal medullary system, which releases the catecholamines adrenaline and noradrenaline almost immediately upon perception of a stressor, mobilising cardiovascular and respiratory resources for the fight or flight response (Wendelaar Bonga, 1997). The second and more sustained axis is the hypothalamic-pituitary-interrenal (HPI) axis, responsible for releasing corticotropin-releasing hormone (CRH) from the hypothalamus upon recognition of a stressor. CRH signals the pituitary to release adrenocorticotropic hormone (ACTH), which stimulates the interrenal cells of the anterior kidney to synthesise and release cortisol, the primary glucocorticoid stress hormone of teleost fish (Guo & Dixon, 2021; Wendelaar Bonga, 1997).

Cortisol and Immune Suppression

Upon release, cortisol fulfils several physiological functions in response to stress. In the short term, it promotes glucose production and fat breakdown to meet the elevated metabolic demands of the stressed organism (Wendelaar Bonga, 1997). Stress also disrupts the permeability of the gill epithelia to water and ions, causing an osmotic imbalance, and cortisol helps to regulate hydromineral balance in response (Wendelaar Bonga, 1997). With regard to immune function, cortisol exerts immunosuppressive effects by inhibiting the production and activity of cytokines, reducing the proliferation and activation of lymphocytes, and downregulating both B cell and T cell responses (Parra et al., 2015; Wendelaar Bonga, 1997). These immunosuppressive effects have been characterised at both the molecular and cellular levels. Parra et al. (2015) established that cortisol diminishes the expression of genes related to B cell activation in the mucosal tissues and reduces the activity of antigen presentation, T cell activation, inflammatory responses, and antiviral responses in salmon skin. Environmental stressors such as temperature changes have also been demonstrated to decrease IgM immunoglobulin concentrations in gill tissue, confirming that cortisol elevation as a result of stress impairs humoral immune capacity at mucosal surfaces (Parra et al., 2015). Yada and Tort (2016) further established that the major categories of stressors, including handling, temperature changes, nutritional stress, overcrowding, and exposure to pollution, all activate the HPI axis and generate receptor-mediated suppression of immune cell function, causing a reduction in disease resistance and an increase in vulnerability to pathogen infection.

Understanding the distinction between acute and chronic stress is important for comprehending the immune consequences of the stress response. Guo and Dixon (2021) demonstrated that chronic stress is consistently immunosuppressive, whilst acute stress produces a more complex and less uniformly negative response. During an acute cortisol spike, certain aspects of innate immune preparedness, such as phagocytic cell mobilisation, may be transiently enhanced before suppression occurs. When stress is sustained, however, as in conditions of persistent crowding, disruption of natural habitat, or poor water quality, chronic immunosuppression ensues, causing disease resistance to decline and opportunistic pathogens to proliferate. These sustained scenarios of immunosuppression represent one of the most significant physiological costs of chronic stress in teleost fish (Guo & Dixon, 2021; Yada & Tort, 2016).

The Stress Reproduction Axis

Stress in bony fish carries significant consequences for the reproductive system, operating directly through the hormonal interaction between the reproductive endocrine system and the stress axis. Wendelaar Bonga (1997) identified the reallocation of energy away from growth and reproduction as a primary consequence of the cortisol-mediated stress response in teleosts, establishing that this redistribution represents one of the most consistent outcomes of HPI axis activation. The elevation of cortisol directly disrupts the hypothalamic-pituitary-gonadal (HPG) axis, through the suppression of gonadotropin-releasing hormone (GnRH) from the hypothalamus, reducing pituitary secretion of luteinising hormone (LH) and follicle-stimulating hormone (FSH), and impairing the synthesis of reproductive hormones including estradiol and testosterone through gonadal steroidogenesis (Wendelaar Bonga, 1997; Yada & Tort, 2016). The cumulative result is an overall reduction in reproductive hormones, compromised gamete production, and diminished reproductive success.

Yada and Tort (2016) confirmed this framework by demonstrating that under sustained stress, physiological and energy resources are redirected away from reproductive and immune functions as the organism prioritises immediate survival. Chronic stress in bony fish therefore results in reduced quality and quantity of eggs and sperm, less consistent spawning, and where applicable, decreased parental investment, with increased susceptibility to reproductive disease and reduced egg survival representing well-recognised consequences in teleost fish populations (Wendelaar Bonga, 1997; Yada & Tort, 2016).

Vulnerability and Recovery

A significant feature of teleost fish is that recovery is possible once stressors have been removed. Bony fish have high reproductive rates with short generation times in comparison to cartilaginous fish, meaning that stress-induced reproductive impairment can be compensated for at the population level if the stressor is removed and environmental conditions improve (Wendelaar Bonga, 1997). However, it must be understood that there is a limit to this resilience, as persistent or intensifying anthropogenic pressures such as pollution, climate change, habitat destruction, and extreme aquaculture practices can exceed the capacity for recovery, specifically for wild bony fish populations and especially for those already under pressure from overfishing or habitat loss.

Table 1 Summary of the main shared and differing immune system features between bony and cartilaginous fish

Feature(s)	Cartilaginous Fish	Bony Fish (Teleost)
Immunological memory	Possess	Possess
Hematopoietic Organs	Leydig organ, Epigonal organ, thymus, and spleen	Anterior kidney, and thymus
Immunoglobulin classes	IgM, IgW and IgNAR	IgM, IgD, and IgT
Gene arrangement of immunoglobulin	Cluster	Translocon
Mucosal lymphoid tissues	GALT, GIALT	GALT, GIALT, SALT, and NALT
Complement pathways	Classic, alternative	Classic, alternative, and lectin
T cell receptor	Use somatic hypermutation and recombination	Recombination only
MHC gene arrangement	On same chromosome	Spread across different chromosomes

5. COMPARATIVE ANALYSIS

5.1 Comparative Summary: Stress and Reproduction in Bony Fish vs. Cartilaginous Fish

The comparison between the two groups, bony and cartilaginous fish, in terms of stress physiology and reproductive vulnerability shows two ancestries that, although different in their mechanisms, hormones that mediate the stress response, and the severity of the population-level consequences, share one basic principle: that constant stress damages both the organism's immunity and reproductive system.

In cartilaginous fish, the main corticosteroid is 1α-OHB rather than cortisol, a hormone whose glucocorticoid action was only recently confirmed through direct observation (Anderson, 2012; Ruiz-Jarabo et al., 2019). The physiological stress responses, including increased corticosteroids, hyperglycaemia, and ionic disturbance, documented by Skomal and Mandelman (2012), were similar to those of teleosts in their general character but differ in terms of the specific hormonal mediators and the absence of tertiary level stress response research in cartilaginous fish as of the time of that review. Most species employ reproductive strategies that are viviparous or involve the laying of large yolky eggs, with gestation periods ranging from several months to just over a year, small litter sizes, and sexual maturity reached only later in life, around a decade or more for the larger species (Carrier et al., 2010; Wheeler et al., 2020). The aftermath of stress-induced reproductive failure, such as premature parturition in captured females, causes a severely detrimental effect on population numbers in cartilaginous fish in comparison to teleosts (Wheeler et al., 2020). A singular event that disrupts the reproductive process in a shark with a two-year gestation period and only two to four pups per litter represents a far greater proportional loss than the same event occurring in a teleost fish capable of producing thousands of eggs for every spawn.

In bony fish, the main stress hormone is cortisol, produced through the HPI axis, with immunosuppressive and anti-reproductive effects that are rapid in onset, receptor-mediated, and fully reversible once the stressor is removed (Guo & Dixon, 2021; Wendelaar Bonga, 1997). The teleost reproductive strategy typically involves many species producing a large number of offspring for every reproductive event, reaching sexual maturity quickly, and the capacity to compensate for losses in reproduction within just one to two breeding seasons. The stress-induced cortisol spike suppresses the HPG axis and reduces reproductive success; however, the population's inherently high rate of increase provides a buffer against the reproductive consequences of time-limited stress (Yada & Tort, 2016).

The disproportion in reproductive biology between the two groups is the reason why the relationship between stress physiology and immune function holds greater conservation significance for cartilaginous fish than for most bony fish. Understanding the 1α-OHB mediated stress response and its negative effects on immune and reproductive systems therefore represents both a scientific priority and a matter of applied wildlife management, with direct implications for improving the population numbers of cartilaginous fish (Carrier et al., 2010; Skomal & Mandelman, 2012; Wheeler et al., 2020).

5.2 Evolutionary Divergence and the Shaping of Two Immune Strategies

Both lineages of the cartilaginous and bony fish had inherited the same foundational architecture of vertebrate adaptive immunity, the immunoglobulins, T cell receptors, and MHC molecules which arose first in the Gnathostomes and has been conserved in one form or another across all jawed vertebrates ever since (Smith et al., 2019). Despite the starting point being together, the 450 million years of separate evolution, under distinct pressures, in specific ecological places, has produced two lineages whose immune system differs significantly through their mechanisms, strategies, and structure.

Cartilaginous fish are the most phylogenetically distant group from mammals that still maintain an immunoglobulin based adaptive immune system, making them important references for understanding what the ancestral vertebrate immune system looked like and how the evolutionary change occurred over time (Mitchell & Criscitiello, 2020). The unique immune features, IgNAR, the cluster organization of immunoglobulin genes, the NARTCR, somatic hypermutation of TCR loci, and the Leydig and epigonal organs are signs of an ancestry that continued to solve the difficulty of surviving in the everchanging marine environment through the set of molecular and cellular tools to those that bony fish subsequently evolved (Smith et al., 2019; Dooley & Flajnik, 2006).

Teleost bony fish, by contrast, demonstrate a more recently differentiated lineage that has undergone extensive genomic expansion, providing the raw material for the progress of a more structurally complex mucosal immune system, a broader complement repertoire, and immunoglobulin classes that specifically adapted to the mucosal surfaces (Smith et al., 2019). The debut of the IgT immunoglobulin as an important mucosal antibody in the group, with no confirmed equivalent to cartilaginous fish, shows the specific demands of a group that has grown into an outstanding range of habitats, from freshwater rivers or deep oceans where exposure to waterborne pathogen of all kinds placed a premium on mucosal defense (Salinas, 2015; Smith et al., 2019).

Understanding this, the immune system of the two groups can be researched and understood not as one being advanced and the other ancient but as two diverse evolutionary solution the same challenges, reproducing and surviving in an aquatic environment full of anthropogenic stressors, parasites and pathogens. There were just different investments of each group; the cartilaginous fish invested in producing unique binding domains that are able to access epitopes that the usual antibodies cannot reach, and diversifying T cell receptors through mechanisms that no other vertebrate has developed (Criscitiello, 2014). The bony fish invested in expanding their mucosal tissue, diversifying their immunoglobulin classes, and developing a broader complement inventory, creating a layered immune response that is quick across many body surfaces (Salinas, 2015; Smith et al., 2019).

5.3 Differences in Disease Resistance and Stress Response

Disease Resistance: What the Evidence Actually Shows

What makes the comparison of disease resistance between cartilaginous and bony fish difficult is the common misconception that sharks and their relatives are resistant to infections and cancer. As discussed in Section 3.3, Garner (2013) wrote that bacterial and parasitic infection were found in 1,546 elasmobranch specimens, as well as neoplasia proving that cartilaginous fish are not immune from infections and neoplastic diseases. There is no evidence that can support the popular but inaccurate claims regarding their disease resistance. Instead, what can be proven is the two differentiating immune strategies and the tools used by the two groups. The single domain VNAR antibody of the cartilaginous fish can reach and bind to parts of a pathogen that conventional antibodies physically cannot access, including enzyme active sites and deep receptor clefts. This offers an advantage that could offer better protection against certain pathogens (Criscitiello, 2014). Early lab work of Walsh et al. (2006) showed that immune cells from the elasmobranch epigonal organ produce soluble factors with antiproliferative effects against human tumor cell lines, this offers the idea that their lymph myeloid tissues may possess properties that can inhibit tumors that has not been identified within teleost fish yet, even though their significance is yet to be confirm in vivo.

In bony fish, the disease resistance is closely related to the integrity of the mucosal immune system and the speed and force at which the IgM and IgT antibodies respond to the entry of a pathogen. The MALT system of teleosts, consisting of GALT, GIALT, SALT, and NALT, provide a layered protection across major body surfaces and compartmentalization of IgT to the mucosal sites when there is an infection demonstrates an intricate and specific response that has not been found in cartilaginous fish (Salinas, 2015; Smith et al., 2019). Considering these factors, bony fish may have the upper hand in the capability of quickly containing infections, while the structural properties of elasmobranch antibodies provide an advantage in other aspects.

What unites the two groups is the most important and crucial fact, the vulnerability that they share when they perceive stress and immunosuppression being the result. In teleosts, heightened cortisol with the HPI axis activation causes a suppression of B cell activation, reducing IgM on mucosal surface and damages antigen presentation and the responses of T cells which causes an increased susceptibility to pathogens (Parra et al., 2015; Wendelaar Bonga, 1997). In cartilaginous fish, the stress response mediated by 1α-OHB causes physiological disruption, as mentioned before the hyperglycemia, ionic imbalance, and acidemia. However, a direct connection to the immune suppression response because of the 1α-OHB increase needs more research, as of now, it is limited (Anderson, 2012; Skomal & Mandelman, 2012). Thus, both groups when experiencing chronic stress represent the main path in which environmental stressors can lead to the increase in disease susceptibility.

Stress Response: Mechanism and Durability

The common denominator of the stress response of the two groups is that the stress perceived sparks hormonal cascades that summon energy and prioritize immediate survival and denying the processes that are not essential such as immune function and reproduction. However, the two differ from the mediators and how well their stress responses have been studied (Wendelaar Bonga, 1997; Anderson, 2012)

Bony fish have the HPI axis and cortisol-controlled stress response that can be found among hundreds of species. There is the differentiation between the acute and chronic stress and how the response affects immunity has been determined. During acute stress, there can be enhanced innate immune parameters before the suppression occurs, while chronic stress causes continuous immunosuppression (Guo & Dixon, 2021). Instead, the bony fish in this sense is quite mapped out, and the side effects on the immune system or reproductive, can be anticipated throughout a range of stressors and their intensities.

In cartilaginous fish, stress physiology is yet to be better understood. Skomal & Mandelman (2012) documented the primary and secondary stress responses to the anthropogenic stressors among elasmobranchs. This showed that the catecholamine, 1α-OHB, and secondary metabolic disturbances are generated in ways that are similar to the teleost response, but tertiary stress response had no specific study at the time of their review. Ruiz-Jarabo et al. (2019) thereafter gave the first verifiable piece of evidence of glucocorticoid action by 1α-OHB, verifying that it produces metabolic responses that are consistent with stress induced glucocorticoid activity. Therefore, this missing piece between the two groups is not necessarily a different biological complexity but instead, a lack of research attention, one that is only in recent years has become noticed.

5.4 Immune Traits, Environmental Adaptation, and Species Survival

How Each Group’s Immune Architecture Supports Survival

The special features of the groups' immune system are not random occurrences. They reflect the specific challenges that the groups had to endure over time and the specific areas in which they live.

The most distinct immune feature for cartilaginous fish can be understood since their ancestry has mainly remained in the oceanic environment throughout their evolution, living in predominantly predatory areas across a wide range of marine habitats. The VNAR domain of IgNAR can penetrate enzyme active sites, and viral receptor clefts could be for pathogens that are particularly difficult to catch perhaps because they had evaded their epitopes in areas unreachable for antibodies (Criscitiello, 2014). The phenomenon of germline joining, where certain antibody configurations are pre-encoded in the genome from birth, represents a strategy that may allow cartilaginous fish to mount rapid responses against repeatedly encountered marine pathogens without requiring the same time-consuming process of recombination on every occasion.

The slow adaptive response in sharks, with the concentrations of specific antibodies present in the blood at a given time, taking anything from weeks to months to develop, suggests that cartilaginous fish could depend on innate mechanisms and the pre-arranged antibody configurations as their first line defense with the adaptive responses primarily for a slower but functional secondary layer (Smith et al., 2019).

For the teleost bony fish, the mucosal immune system with the four specific compartments and mucosal immunoglobulin IgT, shows the needs that have been assigned to a group with such a diverse aquatic habitat around the world, anything from freshwater lakes to river sediments, to tropical water (Salinas, 2015; Smith et al., 2019). The ability to have rapid, compartmentalized mucosal responses, especially with IgT increasing at the sites of infections and IgM remaining the same, suggests a level of immunologically accuracy at the mucosal surface that has been quite adapted to such a diverse group that faces consistent and varied exposure to pathogens (Salinas, 2015). The complement system with the lectin pathway that is not present in cartilaginous fish, allows teleosts an extra swift response humoral mechanism that is able to identify and destroy pathogens without needing prior antibody production (Nonaka & Smith, 2000).

Immunity and Survival in a Changing Marine Environment

Both groups are now facing a fast-paced environmental change due to anthropogenic activity, with the ocean warming, pollution, and overfishing, the immune consequences of these stressors are becoming and are of scientific concern. The relationship between the immune system and stress, where consistent environmental disruption increases stress hormones, then suppressing immune function means that any environmental stressor that is intense enough to chronically activate the HPI axis in teleosts or the equivalent axis in elasmobranchs, could increase the pathogen susceptibility, ruin reproductive success and damage the chance at population recovery (Yada & Tort, 2016; Wendelaar Bonga, 1997).

For bony fish, the relatively high reproductive rates and short generation times of a large variety of species provides some population level resilience to smaller, and time limited stressors, even though this strength is not unlimited and is already reaching the limit in commercially exploited populations (Wendelaar Bonga, 1997). The immunosuppression that occurs from chronic stress in teleosts are understood well enough to allow management, including things such as better aquaculture conditions, controlled fishing practices, and higher environmental quality standards, can be designed with the knowledge of these physiological consequences.

For cartilaginous fish, the conservation stakes are substantially higher than those of bony fish. Their reproductive strategy documented by Carrier et al. (2010) with the late sexual maturity, small litter sizes, and the long gestation periods, signifies that the reproductive failure due to stress has disproportionate and long-lasting effects on the population viability. Wheeler et al. (2020) also documented that stress from captures, causes premature parturition in pregnant females, proving a direct and instant effect on the reproductive system, affecting the population numbers. This, with the documented immunosuppressive effect of the corticosteroid increase, creates a situation in which anthropogenic stressor can interact synergistically to damage the immune and reproductive health of cartilaginous fish at the same time.

In the end, the comparative analysis of bony fish and cartilaginous fish immune system uncovers that those evolutionary differences have produced two distinct and orderly immune starters shaped by different phylogenetic histories, different ecological trajectories, and different life history constraints. Studying and understanding both strategies and the ways that environmental pressure can impact them is crucial for advancing comparative immunology and educating on the conservation of the two groups that symbolize the full diversity of jawed fish in the world.

6. **Conclusion**

The comparative analysis presented in this thesis demonstrates that although cartilaginous and bony fish share the basic components of jawed vertebrate immunity, they have evolved along distinct immunological trajectories over 450 million years of independent evolution. The key findings of this review highlight not only the structural and functional differences between the two groups, but also the broader biological principles that govern how immune and stress systems interact to determine survival and adaptation in the marine environment.

Three principal insights emerge from this analysis. The first concerns the structural divergence of their immune systems: cartilaginous fish rely on the IgNAR single-domain antibody and the NARTCR, whilst bony fish have developed a multi-layered mucosal immune system, each reflecting the distinct evolutionary and ecological pressures experienced by each group. The second concerns the stress-immune axis: in both groups, chronic anthropogenic stressors exert significant physiological effects that extend beyond immediate survival, causing immunosuppression and reproductive impairment that directly increases population-level vulnerability. The third concerns the disproportionate conservation sensitivity of cartilaginous fish: given their limited tertiary stress response research, K-selected reproductive strategy, and slow population recovery rates, the importance of expanding research on this group cannot be overstated.

The unique structural properties of elasmobranch antibodies, particularly the IgNAR, represent a promising avenue for therapeutic antibody development, with potential biomedical applications that are only now beginning to be explored. The well-characterised cortisol-mediated stress response of teleost bony fish provides a validated physiological framework against which the elasmobranch stress system, with its comparatively limited research base, can be progressively developed and understood.

Regarding future research, there are several important directions to be pursued. Future research should prioritise investigation of the tertiary stress response in elasmobranchs, examining how 1α-OHB elevation affects specific immune parameters and reproductive hormone levels in vivo. This would substantially address the knowledge gap between teleost and elasmobranch stress physiology. Integrating stress physiology, immune system function, and reproductive biology into a unified conservation framework for threatened elasmobranch species would permit the development of management plans that fully account for the biological complexity of these animals.

Ultimately, this thesis argues that understanding the immune and stress systems of marine fish is not merely a scientific pursuit but a practical necessity. As anthropogenic pressures on marine environments continue to intensify, the survival of cartilaginous fish, including sharks and rays, as well as their teleost counterparts, will depend in part on our capacity to understand their physiology well enough to protect it.

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