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REVIEW PAPER

Temperature effects on teleost immunity in the light of climate change

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Abstract

Temperature is an important environmental modulator of teleost immune activity. Susceptibility of teleosts to temperature variation depends on the species-specific adaptive temperature range, and the activity of the teleost immune system is generally temperature-dependent. Similar to many physiological and metabolic traits of ectotherms, temperature modulates the activity of immune traits. At low temperatures, acquired immunity of many teleost species is down-modulated, and their immuno-competence mainly depends on innate immunity. At intermediate temperatures, both innate and acquired immunity are fully active and provide optimal protection, including long-lasting immunological memory. When temperatures increase and reach the upper permissive range, teleost immunity is compromised. Moreover, temperature shifts may have negative effects on teleost immune functions, in particular if shifts occur rapidly with high amplitudes. On the contrary, short-term temperature increase may help teleost immunity to fight against pathogens transiently. A major challenge to teleosts therefore is to maintain immuno-competence throughout the temperature range they are exposed to. Climate change coincides with rising temperatures, and more frequent and more extreme temperature shifts. Both are likely to influence the immuno-competence of teleosts. Nonetheless, teleosts exist in habitats that differ substantially in temperature, ranging from below zero in the Arctic's to above 40°C in warm springs, illustrating their enormous potential to adapt to different temperature regimes. The present review seeks to discuss how changes in temperature variation, induced by climate change, might influence teleost immunity.

KEYWORDS
acquired immunity, climate change, immune competence, innate immunity, pathogen, teleost, temperature

1 | INTRODUCTION

Fish-immunology research provides accumulating evidence that temperature is a strong environmental modulator of fish immunity. Climate change affects temperature regimes in aquatic habitats and accordingly fish immune responses. The present review summarises the current knowledge about temperature effects on immunity of fish, and aims to evaluate how climate change may alter immune responses of fish and their interaction with pathogens and parasites.

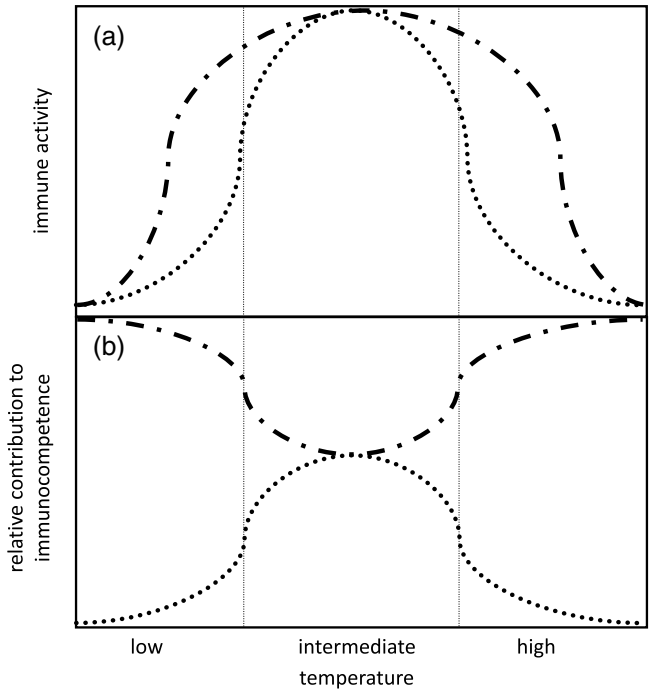

FIGURE 1 Scheme of temperature effects on teleost immunity. (a) Temperature dependence of the activity of innate (dashed line) and acquired immunity (dotted line) and (b) relative contribution of innate and acquired immunity to the overall immuno-competence at given temperatures. At low temperatures, activity of innate and acquired immune traits is reduced. Whereas acquired immunity is supressed at low temperatures, innate immunity remains more active and responsive. At low temperatures, immuno-competence depends more on innate immune functions. With rising temperature, activity of both innate and acquired immunity goes up. At intermediate temperatures (of a given teleost species) acting in concert innate and acquired immunity are active and maintain immuno-competence. Information on how teleost immunity responds to high temperatures is scarce. Here, it is hypothesised that acquired immunity is more susceptible to high temperature and that innate immunity more robust. Accordingly, immuno-competence at high temperatures would depend more on innate immune traits (— · ·) innate immunity; (·····) acquired immunity

The global average temperature is predicted to increase by 1.5°C above the pre-industrial level by 2050 (Ipcc, 2014; Masson-Delmotte *et al.*, 2018). Climate change coincides with extreme weather events, such as heavy rainfalls, temperature shifts and heat waves (*e.g.*, Bennett *et al.*, 2019; Cartwright, 2019; Naveendrakumar *et al.*, 2019). Climate models predict an increase in the number of extremely hot days, whereby the highest temperature increase is expected in the tropics. In some geographic regions warming occurs more rapidly as the global average, *e.g.*, continents warm up faster than oceans. In the Artic regions, warming is predicted to be 2–3 times more pronounced as the global average (Masson-Delmotte *et al.*, 2018).

Teleost species are widely distributed and adapted to the temperature conditions in their natural environments. This ranges from temperatures below 0°C in the polar regions to >38°C in warm springs, and includes habitats with low and high temperature variation (Wootton, 1999). Accordingly, a temperature that is optimal for one species might be detrimental to another, and a change of average temperatures by just 1°C might be well handled by one species, but might be critical for another. Whereas eurythermal teleost species are likely to have a higher potential to adapt to changes in temperature regimes, stenothermal species are presumably more vulnerable (Ream *et al.*, 2003).

The huge diversity of teleosts and their variability in temperature adaptations makes it difficult to develop appropriate verbalisation of what might be a strong or not-so-strong temperature effect on fish immunity. Each teleost species is adapted to a temperature range, which can be narrow or wide, at the lower or upper end of the temperature range inhabited by teleosts. For the present review we would like to divide each species-specific temperature range in three parts: "low," "intermediate" and "high" temperature (Figure 1).

In accordance with a physiological temperature optimum (Pörtner & Knust, 2007), immune systems of teleosts perform optimally at intermediate temperatures within the species-specific temperature range (Abram *et al.*, 2017; Bowden, 2008; Kollner *et al.*, 2002; Kollner & Kotterba, 2002; Sepahi *et al.*, 2013; Sirisena *et al.*, 2019; Swain & Nayak, 2009; Van Muiswinkel, 2019) (Figure 1). The teleost immune system is endowed with the key elements of a vertebrate immune system (Flajnik, 1996; Magnadottir, 2010; Sunyer, 2013; Van Muiswinkel, 2019). The innate immune system is the first line of defence, with an array of evolutionary highly conserved molecules for pathogen recognition, opsonisation and elimination. The second line of defence is the adaptive (or acquired) immunity, which generates highly specific antibody responses and long-lasting immunological memory (Flajnik, 1996). The interaction of these two lines of defence of the teleost immune system and therewith its efficiency is shaped by the environmental temperature (Abram *et al.*, 2017; Barraza *et al.*, 2021; Bengten *et al.*, 2006; Bowden, 2008; Ellis, 2001; Grayfer *et al.*, 2018; Magnadottir, 2010; Miller *et al.*, 1998).

Due to disease outbreaks in aquaculture systems such as winter saprolegniosis and bacterial cold-water disease, effects of cold temperatures on fish immunity are well studied (Bly *et al.*, 1992; Ibarz *et al.*, 2010; Quiniou *et al.*, 1998; Tort *et al.*, 1998a; Tort *et al.*, 1998b). Possible effects of high temperatures on teleost immunity and effects of rapid temperature shifts are only recently coming into focus of fish immunology research. Both temperature extremes and temperature shifts are expected to become more frequent with global climate change, possibly leading to reduced immuno-competence of vertebrates and potentially the spread of infectious diseases. The present review will start with overviews on teleost immune functions and how these respond and adapt under temperature variation. Subsequently potential effects of climate change–induced temperature effects, such as heat waves and temperature shifts, will be discussed. Finally, aspects of adaptations of teleost immunity to changing temperature regimes will be discussed.

2 | TELEOST IMMUNITY IS MODULATED BY TEMPERATURE

At cold conditions, activity of the immune systems of ectotherms is down-modulated. Accordingly, maintenance of immuno-competence in the cold is challenging for teleosts. Interestingly, traits of innate and

acquired immunity respond differentially along temperature gradients, which might be crucial when temperatures decrease.

When temperatures decrease, both traits of innate and acquired immunity are down-modulated. Lower temperatures decreased leukocyte activation and dampened their mobilisation (Kollner & Kotterba, 2002). Innate immune traits such as the respiratory burst activity of phagocytes and complement activity decreased at lower temperatures (Nikoskelainen *et al.*, 2004). Similarly, phagocytic activity and intracellular killing decreased at lower temperatures (Scott *et al.*, 1985; Sohnle & Chusid, 1983). Nonetheless, the examination of the expression of a range of antiviral immune genes showed differential responsiveness to temperature (Dios *et al.*, 2010). Although some antiviral genes were almost completely inhibited by low temperature (IFNγ, IFR3, MDA-5, MX), other innate immune genes remained active (TLR3, IL-1β, iNOS, TNF-α) (Dios *et al.*, 2010).

Active innate immune functions at relatively low temperatures were described in many fish species tested [*e.g.*, tench (*Tinca tinca*) (Collazos *et al.*, 1995), channel catfish (*Ictalurus punctatus*) (Ainsworth *et al.*, 1991; Dexiang & Ainsworth, 1991) or three-spined stickleback (*Gasterosteus aculeatus*) (Scharsack *et al.*, 2016)]. Accordingly, it was suggested that teleost immunity at low temperatures might depend on innate immune traits. Indeed, immunity of sockeye salmon (*Oncorhynchus nerka)* relied on innate functions, such as complement activity and phagocytes at 8°C, whereas the specific immune response (antibody production and lymphocyte proliferation) was accelerated at a rearing temperature of 12°C (Alcorn *et al.*, 2002). Similarly, brown trout (*Salmo trutta*) were able to develop a specific and strong antibody response between 9°C and 15°C, but not below 9°C (O'Neill, 1980).

In common carp (*Cyprinus carpio)* lowering temperature from 20°C to 8°C induced a delay in the primary antibody response, but had no effect on its magnitude. The anamnestic character of the secondary immune response was present from 24°C to 20°C, but was lost at 18°C and below (Rijkers *et al.*, 1980; Rijkers *et al.*, 1981). Numbers of blood granulocyte like cells increased in carp at low temperatures, and it was suggested that the non-lymphoid (non B- and T-cells) defence becomes more important when circumstances become less favourable for acquired immunity and antibody formation (Rijkers *et al.*, 1981).

In sum, acquired, highly specific immunity is active at the species-specific intermediate temperature range and is supressed at low temperatures (Bly & Clem, 1991; Einarsdottir *et al.*, 2000; Hardie *et al.*, 1994; Le Morvan *et al.*, 1996; Tort *et al.*, 1998a) (Figure 1a). Innate immune activity decreases as well with temperature, but remains active at low temperatures and compensates the suppression of acquired immunity at low environmental temperatures to some extent, and thus enables teleosts to remain immuno-competent in the cold (Ainsworth *et al.*, 1991; Alcorn *et al.*, 2002; Bowden *et al.*, 2007; Ellis, 2001; Le Morvan *et al.*, 1996; Le Morvan *et al.*, 1998; Le Morvan-Rocher *et al.*, 1995; Nikoskelainen *et al.*, 2004) (Figure 1b).

2.1 | Vaccination

The fact that acquired immunity of fish is supressed at low temperatures has an important economical implication, because vaccination of aquaculture fish stocks at low temperatures prevents the desired protection. For example, in rainbow trout, bath vaccination against *Yersenia ruckeri* induced protection only when performed at 15°C, but not at 5°C and 25°C (Raida & Buchmann, 2008).

Investigations on the underlying mechanisms suggest that lower activity of the immune-regulatory network at low temperatures causes reduced responsiveness. In rainbow trout (*Onchorhynchus mykiss*), immune regulatory genes (IL1, IL10, IFN) were responding to immunisation with bacteria (*Y. ruckeri*) much slower and with a lower magnitude at 5°C compared to 15°C and 25°C (Raida & Buchmann, 2007). The authors suggest that insufficient cytokine stimulation contributes to the lacking ability to establish protection against *Y. ruckeri* after vaccination at low temperatures (Johnson *et al.*, 1982; Raida & Buchmann, 2008; Rodgers, 1991).

A study in rainbow trout found that the major histocompatibility complex two (MHC II) receptor system, a key element of acquired immunity, was downregulated at cold temperature (Nath *et al.*, 2006). Functional MHC II would present pathogen-derived peptides to T-lymphocytes, which mediate the activation of B-lymphocytes, to produce immunoglobulins (antibodies), the main effector molecules of acquired immunity. In bluegill (*Lepomis macrochirus*), Cuchens and Clem *et al.* (1977) observed reduced responsiveness of T-lymphocytes at cooler temperatures, while activity of B-cells remained high. Because T-cells are central in the mediation and upregulation of acquired immunity, Cuchens and Clem *et al.* (1977) suggested that the suppression of acquired immunity in the cold was mainly attributed to reduced responsiveness of T-lymphocytes (Clem *et al.*, 1977).

An important aspect of temperature susceptibility of such receptor-mediated responses of B and T-cells seems to be the membrane fluidity (see also below the chapter on "section 5.1"). Low temperatures reduce the membrane fluidity of cells, which inhibits mobility and aggregation (capping) of membrane bound (immune) receptors (MHC II and others) and therewith the transmembrane signal transmission and cell activation (Bly & Clem, 1992; Le Morvan *et al.*, 1998). Taken together, low temperature seems to slow down signalling and activation pathways of acquired immunity in many fish species to such an extent that acquired immunity, and accordingly vaccination, is less efficient. For example in Nile tilapia (*Oreochromis niloticus*) vaccinated at 25°C and 29°C, > 90% survived the corresponding challenge with *Streptococcus agalactiae*, whereas vaccination at 21°C resulted only in 70% survival (Wang *et al.*, 2020). As a consequence, aquaculture management needs to seek out (seasonal) time windows with temperatures sufficiently high to facilitate immunisation through vaccination of the respective fish stock. Another possible consideration for improvement of vaccination success might be a moderate temperature increase during the immunisation phase.

2.2 | Pathogens

Several pathogens take advantage from the low/slow responsiveness of teleost acquired immunity in the cold. Thus, cold periods can cause disease problems in aquaculture systems when opportunistic pathogens (bacteria, fungi) spread in fish stocks (Bly *et al.*, 1993; Contessi

TABLE 1 List of fish species referred to in the present review

Species	Temp. tested	Main result	Reference	Temp. range in fish base
Emerald rockcod (*Trematomus bernachii*)	1°C	Antibody response at 1°C	Buonocore *et al.*, 2016	−1.8°C to −0.7°C
Antarctic bullhead (*Notothenia coriiceps*)	1°C	Response to immunisation at 1°C	Ahn *et al.*, 2016	−1.7°C–2.4°C
Atlantic cod (*Gadus morhua*)	10°C, 16°C	Innate anti-viral immunity higher at 10°C than at 16°C	Inkpen *et al.*, 2015	0°C–15°C
	1°C, 7°C, 14°C	Lowest mortality upon infection at 7°C compared to 1°C and 14°C	Magnadottir *et al.*, 1999	
Winter skate (*Leucoraja ocellata*)		Evolutionary fast adaptation to temperature changes is mediated by epigenetic mechanisms	Lighten *et al.*, 2016	1.5°C–14.4°C
Black rockfish (*Sebastes schlegelii*)	16°C– 5°C, 16°C–27°C	Temperature shifts cause stress and inflammatory responses	Lyu *et al.*, 2018	8°C–21°C
Sea bass (*Dicentrarchus labrax*)		Immune parameters show seasonal variation	Pascoli *et al.*, 2011	8°C–24°C
Gilthead seabream (*Sparus aurata*)	18°C, 22°C	Thermal imprinting as larvae was detectable in adults	Mateus *et al.*, 2017	12.1°C–21°C
Broad-nosed pipefish (*Syngnathus typhle*)		Lacks MHC class II receptors	Haase *et al.*, 2013	8°C–24°C
Olive flounder (*Paralichthys olivaceus*)	10°C, 20°C	Temperature shift from 10°C to 20°C reduced mortality by HIRR virus	Wang *et al.*, 2021	8.6°C–25°C
		Innate immunity upregulated upon acute heat stress	Yuan *et al.*, 2021	
	12°C–20°C *in vivo*	Innate immunity active at 20°C and mild hypoxia	Zanuzzo *et al.*, 2020	
Atlantic salmon (*Salmo salar*)	10.5°C, 13.5°C, 16.5°C *in vivo*	Innate anti-viral immunity higher at 10.5°C than at 13.5°C and 16.5°C	Ignatz *et al.*, 2020	2°C–9°C
Sockeye salmon (*Oncorhynchus nerka*)	8°C, 12°C	Relied on innate immunity at 8°C, adaptive immunity active at 12°C	Alcorn *et al.*, 2002	0°C–25°C
Rainbow trout (*Onchorhynchus mykiss*)	5°C, 15°C, 25°C	Antibody response at 15°C, but not at 5°C and 25°C	Raida & Buchmann, 2007, 2008	10°C–24°C
	8°C, 23°C	Adapt to local temperature regimes	Verleih *et al.*, 2015	
	4°C	Anti-viral response still active at 4°C	Abram *et al.*, 2019	
Brown trout (*Salmo trutta*)	4°C, 9°C, 15°C	Antibody response delayed below 9°C	O'Neill, 1980	18°C–24°C
Arctic char (*Salvelinus alpinus*)	1°C *in vitro*	Innate anti-viral immunity still active	Semple *et al.*, 2017	4°C–16°C
Three-spined stickleback (*Gasterosteus aculeatus*)	13°C, 18°C, 24°C (*in vivo* and *in vitro*)	*In vivo* -> *in vitro*, cold to warm temperature shift deteriorates responsiveness of phagocytes	Scharsack *et al.*, 2016	4°C–20°C
	13°C, 18°C, 24°C, 28°C	Heat waves cause immunological disorders	Dittmar *et al.*, 2014	
	9°C, 12°C, 15°C, 18°C, 21°C, 24°C	Defence of tapeworm infections strongest in the range of 9°C–15°C	Franke *et al.*, 2017, 2019;	
	17°C, 21°C	Lifelong adaptation to temperature becomes transgenerationally plastic	Shama *et al.*, 2014, 2016	
Tench (*Tinca tinca*)	12°C, 22°C 30°C	Innate immunity active at low temperature, seasonal changes in immune activity	Collazos *et al.*, 1995	4°C–24°C

TABLE 1 (Continued)

Species	Temp. tested	Main result	Reference	Temp. range in fish base
Channel catfish (*Ictalurus punctatus*)	4°C–30°C	Membrane fluidity is susceptible to temperature shifts and receptor mediated responses	Bly *et al.*, 1986	10°C–32°C
Nile tilapia (*Oreochromis niloticus*)	21°C, 25°C, 29°C, 33°C	Vaccination at 25°C–29°C caused >90% protection; protection was lower after vaccination at 21°C and 33°C	Wang *et al.*, 2020	14°C–33°C
Common carp (*Cyprinus carpio*)	8°C, 18°C, 20°C, 24° C, 28°C	Faster antibody responses at warmer temperature	Rijkers *et al.*, 1980, 1981	3°C–35°C
	20°C–8°C	Temperature shift from 20°C to 8°C 8 days post immunisation prevented antibody response	Avtalion, 1969	
Bluegill (*Lepomis macrochirus*)	22°C, 32°C (*in vitro*)	Low temperature suppression of acquired immunity depends on regulatory T-cells rather than B-cells	Cuchens & Clem, 1977	1°C–36°C
		Temperature drops 10°C/24 h are immune-suppressive	Bly & Clem, 1991	
Japanese medaka (*Oryzias latipes*)	25°C, 30°C	Temperature shift from 25°C to 30°C deteriorates phagocyte responses	Prophete *et al.*, 2006	18°C–24°C
Zebrafish (*Danio rerio*)		3°C higher thermal preference upon immunisation	Rey *et al.*, 2017; Boltana *et al.*, 2018	18°C–24°C

et al., 2006; Ibarz *et al.*, 2010; Nath *et al.*, 2006). Some viruses are specifically adapted to infect fish at low temperatures. The viral haemorrhagic septicaemia virus (VHSV) is an infectious disease of rainbow trout, which causes huge losses in aquaculture industries. It causes high mortality at relatively low temperatures around 10°C, but fails to cause severe pathology above 15°C (Escobar *et al.*, 2018; Hershberger *et al.*, 2013; Sano *et al.*, 2009). Lorenzen *et al.* (2009) showed that rainbow trout were capable of producing protective antibodies against VHSV 36 days after vaccination at 15°C, but were unable to do so at 5°C and 10°C.

Similarly, the spring viremia of carp (SVC) can cause high mortality in carp aquaculture, typically in spring when temperatures range from 10°C to 17°C. At higher temperatures, carp develop humoral immunity, which provides protection against reinfections (Ahne *et al.*, 2002). Another example is the infection of olive flounder (*Paralichthys olivaceus*) with the Hirame novirhabdovirus (HIRRV) in which a temperature shift from 10°C to 20°C significantly reduced mortality. Prolonged exposure of infected flounders to 20°C resulted in robust antibody-mediated immunity against reinfection with HIRRV (Wang *et al.*, 2021). This suggests that viral pathogens such as VHSV, SVC and HIRRV have adapted to infect, proliferate and cause pathology (and even mortality) in their hosts at relatively low temperatures, taking advantage from their hosts' less active acquired immune system.

On the contrary, teleosts are not completely unprotected against viral infections at low temperatures. A fibroblast cell line from a cold-adapted teleost, the Arctic char (*Salvelinus alpinus*) expressed MHC I receptors at a temperature as low as 1°C and maintained resistance against viral infection (CSV, IPNV) at 4°C (Semple *et al.*, 2017). Similarly, in rainbow trout the endogenous antigen processing and presentation pathway (EAPP) for antiviral defence was still constitutively expressed at 4°C, but not inducible though (Abram *et al.*, 2019). In Atlantic salmon (*Salmo salar*) innate antiviral biomarker genes were strongly upregulated at 10.5°C compared to 16.5°C, in response to a viral mimic (polyriboinosinic polyribocytidylic acid – pIC) injection (Ignatz *et al.*, 2020). In Atlantic cod (*Gadus morhua*) genes of the interferon pathway responded faster (6 h) to pIC challenge at 16°C compared to 10°C, but later (24 h) responses at 10°C exceeded those at 16°C (Inkpen *et al.*, 2015) (see Table 1 for overview). Taken together (innate) antiviral immunity is still active at low temperatures in fish, but the immune response to viral pathogens decreases at low temperatures. With rising temperature acquired immunity becomes more active and mediates specific immunity and immunological memory against viral infections.

3 | TEMPERATURE ADAPTATIONS OF TELEOST IMMUNITY

Acquired immunity of teleosts appears to be low-, or even non-responsive, at low temperatures on multiple levels ranging from immune mediators and receptor–ligand interaction to the production of effector molecules. Acquired immunity is a costly trait and at low

temperature, the cost/benefits balance might be shifted as the pathogen activity slows down with temperature too.

Most fish species investigated for effects of low temperature on acquired immunity (*e.g.*, *C. carpio*, *O. mykiss*, *Sparus aurata*, *I. punctatus*) originate from temperate regions with distinct seasonality (*i.e.*, cold winters, warm summers). In such species, possibly the down-regulation of acquired immunity is also a response to winter conditions with reduced availability of nutrients and the need to save energy *vs*. nutrient-rich summer conditions with high metabolic conversion rates and high infection pressure, demanding quick immune responses.

3.1 | Teleost immunity adapts to cold conditions

A whole clade of cold-adapted teleosts, the cod-like fish (Gadidae) have lost parts of the adaptive immune system, namely MHC II receptor system (Malmstrom *et al.*, 2016; Star *et al.*, 2011). MHC II presents pathogen-derived peptides to T-cells, which activate B-cells to produce antibodies. Also Syngnathid, the broad-nosed pipefish (*Syngnathus typhle*), is immuno-competent without MHC II receptors (Haase *et al.*, 2013). Such variation in teleost immune systems might be facilitated by lower infection pressure at low temperature. This is contradicted by diseases such as winter saprolegniosis, bacterial cold-water disease and some viral infections that specifically harm teleosts at cold conditions. Nonetheless, these diseases seem to be important mainly in (freshwater) aquaculture systems with much higher fish–host density compared to wild populations.

Not all teleost species lose acquired immune activity in the cold. Species that are adapted to extremely cold conditions, like the Antarctic notothenoid (*Trematomus bernachii*) (cold-stenothermic), are endowed with an immune gene repertoire comparable to other teleosts (Coscia & Oreste, 2009; Gerdol *et al.*, 2015; Giacomelli *et al.*, 2015) and keep acquired immune activity in the cold. Immunoglobulins of Antarctic fish show adaptations, especially in their hinge regions, which allow molecular flexibility in extremely cold temperatures (Coscia *et al.*, 2011; Pucci *et al.*, 2003), reviewed by Flajnik (2018). *T. bernachii* were successfully immunised against bacteria (*Phsychrobacter* sp.) at temperatures as low as 1°C (Buonocore *et al.*, 2016). Similarly, RNA transcripts from Antarctic bullhead (*Notothenia coriiceps*) showed an immune-gene response to heat-killed bacteria at 1°C, representing antigen processing and presentation (Ahn *et al.*, 2016). The antibody response at 1°C took relatively long, titres were significant only 60 days post immunisation (Buonocore *et al.*, 2016), compared to carp at 28°C which mounted an antibody response after 8 days (Rijkers *et al.*, 1981) (Table 1). Nonetheless, the notothenoid examples illustrate that an adaptive immune response is possible at extremely low temperatures.

The fact that some fish species lose acquired immune traits whereas others keep them even at very low temperatures suggests that not temperature alone modulates the cost/benefits balance of acquired immunity. In less extreme environments, tolerance to pathogens might outweigh the costs for acquired immunity (Gadids, Syngnathids), whereas in more extreme environments, tolerance might be costlier than maintenance of acquired immunity (Notothenoids). In the latter example, temperature conditions are very stable (cold-stenothermic) while Gadids and Syngnathids are exposed to some temperature fluctuations. Nonetheless, aspects of tolerance to pathogen infections are yet understudied in teleosts. It would be interesting to investigate if temperature adaptation coincides with patterns of tolerance; for example, do stenothermic teleosts differ in tolerance from euryhtermic ones and can general patterns be identified?

3.2 | Intermediate temperature

At intermediate temperatures of the species-specific temperature ranges, teleost immune systems respond fast and specific (Bengten *et al.*, 2006; Cuchens & Clem, 1977; Ellis, 2001), cell-mediated cytotoxicity (CMC) is mobilised (Fischer *et al.*, 1999) and innate and acquired immunity of teleosts performs optimally together (Bowden *et al.*, 2007; Kollner & Kotterba, 2002; Magnadottir, 2010; Van Muiswinkel, 2019) (Figure 1). Accordingly, the success of vaccination of teleosts is best at a species-specific intermediate temperature (Van Muiswinkel & Wiegertjes, 1997).

Similar to mammals, the immune system of teleosts is more and more understood as a complex network of innate and acquired immune components and regulatory factors (Bird *et al.*, 2006; Buchmann, 2012; Rebl & Goldammer, 2018). Presumably many, if not all, components of such immunological networks in teleosts are temperature-dependent and interact optimally at a species-specific intermediate temperature.

3.3 | Behavioural fever

The strategy of ectothermic species to move to warmer microhabitats after infection to increase their body temperature and thus accelerate their immune defence "behavioural fever" (Reynolds *et al.*, 1976) is well represented in teleosts. Mortality of experimentally infected fish was strongly reduced if the fish were allowed to search their thermal preference (Cerqueira *et al.*, 2016; Covert & Reynolds, 1977; Rakus *et al.*, 2017). In zebrafish (*Danio rerio*) even a simulated challenge using inactive viral antigens caused a 3°C upward shift of their thermal preference (Boltana *et al.*, 2018; Rey *et al.*, 2017), indicating the high level of conservation of behavioural fever in teleosts. Interestingly, the carp herpes virus (CyHV-3) seems to have evolved counter-measures to behavioural fever. The virus expresses a soluble decoy receptor for tumour necrosis factor alpha (TNF-α). This receptor binds the TNF-α produced by the infected carp, which had a negative effect on the expression of behavioural fever and allowed the virus to multiply (Rakus *et al.*, 2017).

Behavioural fever is an elegant way for teleosts [and many other cold-blooded animals (Catalan *et al.*, 2012; Hunt & Charnley, 2011; Todd *et al.*, 2016)], to actively maximise the efficiency of their immune systems. Consequently, moderate warming might also provide advantages to immunity of ectotherms, including teleosts. On the contrary, the ability of fish to choose adequate temperature areas can help

them to minimise temperature stress, *e.g.*, avoidance of temperature shifts in stagnant shallow or surface waters by movement to deeper, more temperature stable areas.

3.4 | High temperature

Most studies of temperature effects on teleost immunity focus on the permissive temperature range for the respective species investigated and find optimal performance at intermediate temperatures. Yet, high temperature, that is still tolerable but exceeds the optimum range, has hardly been investigated with respect to its effect on immunity. In the face of climate change and global warming, a critical question is, how does the teleost immune system perform at temperatures above the optimal range of a species?

Figure 1 suggests that innate immunity is more robust at rising temperatures compared to acquired immunity, because its pathways and effector mechanisms are less complex. Accordingly, innate immunity might contribute relatively more to teleost immuno-competence beyond the species' temperature optimum, similarly to what was observed at low temperatures. Empirical evidence of immune responses at the upper scale of teleost's temperature optimum is sparse. A study in Atlantic salmon revealed that innate immunity was not affected by high temperature (20°C) in combination with mild hypoxia (*c.* 65%–75% air saturation) (Zanuzzo *et al.*, 2020). Nonetheless, the hypothesis that the teleost innate immune system is more robust at high temperature, as suggested by the present review, awaits further investigation.

4 | HEAT WAVES

Periods of high temperatures (heat waves) have become more frequent in recent years. Exposure of teleost to heat is affecting its multiple functions, including metabolic, physiological, respiratory, reproductive and immunological traits. These traits may directly be affected by rising temperatures, but they are also connected with one another, and thermal stress that affects physiology and respiration in the first place may also indirectly affect other traits such as immunity.

4.1 | Heat stress

Three-spined sticklebacks experimentally exposed to a heat wave without pathogenic challenge exhibited swollen spleens and excessive respiratory burst activity of their head kidney leukocytes. This condition was presumably caused by thermal stress that affected metabolic and physiological traits and caused cell death and degradation (Dittmar *et al.*, 2014). A transcriptomics study, also without pathogenic challenge, in olive flounder (*P. olivaceus*) observed upregulation of innate immunity after exposure to acute heat stress (Yuan *et al.*, 2021). These studies illustrate that teleost immune functions are affected by heat stress, and it was hypothesised that this might be detrimental to immuno-competence (Dittmar *et al.*, 2014).

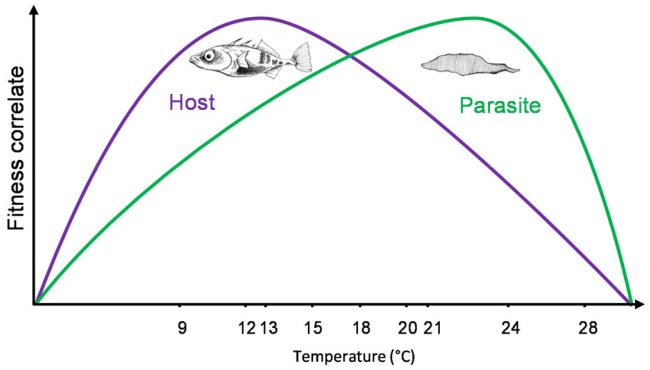

FIGURE 2 Stickleback-tapeworm-temperature interaction. Effect of temperature on fitness correlates of the three-spined stickleback and its tapeworm parasite *Schistocephalus solidus*. Sticklebacks and *S. solidus* were laboratory offspring from different local pairs (origins) and experimentally exposed to temperature variation. Fitness correlates of sticklebacks were immune activity and body condition indices, including a gonado-somatic index and of S. solidus, its weight increase and the production of eggs and viable larvae. Temperatures 9°C, 12°C, 15°C, 18°C, 21°C and 24°C were tested with four stickleback-parasite origins (Franke *et al.*, 2019), 13°C and 24°C with two origins (Franke *et al.*, 2017), 15°C and 20°C with one origin (Macnab & Barber, 2012) and one study used uninfected sticklebacks at 13°C, 18°C, 24°C and 28°C (Dittmar *et al.*, 2014)

4.2 | Heat and infections

Indeed, some evidence suggests that teleosts become more vulnerable to infections when temperatures increase. A cold-adapted species, the Atlantic cod (*G. morhua*), seems to be immunocompromised already at 14°C. During a 12 month temperature experiment, cod suffered from infections with parasites (*Loma morhua*), fungi (*Ichthyophonus hoferi*) and bacteria (*Aeromonas salmonicida achromogenes*) (Magnadottir *et al.*, 1999). Highest mortalities up to 48% occurred at 14°C, followed by 12% at 1°C and at 7°C only 6% of the cod died, suggesting that cod immunity was optimal around 7°C. These data underline that cold-adapted teleost species such as Atlantic cod are highly susceptible to rising temperature.

In temperate regions fish are also susceptible to warming. During the 2003 European heat wave three-spined sticklebacks (*G. aculeatus*) were investigated in an outdoor enclosure experiment. High mortalities occurred in enclosed sticklebacks and were attributed to high parasite burden of moribund fish as a consequence of immunological disorders due to high temperatures. Surviving sticklebacks had fewer parasites than moribund ones and were endowed with intermediate numbers of alleles of MHC II receptor genes (Wegner *et al.*, 2008). Previous experimental parasite infections had illustrated that sticklebacks with intermediate numbers of MHC II alleles (4–5) were more resistant than those with high (7–8) and low (2–3) numbers of alleles (Wegner *et al.*, 2003).

Interestingly, sticklebacks that survived the 2003 European heat wave had intermediate optimal numbers of MHC II alleles and lower parasite burden (Wegner *et al.*, 2008), suggesting that temperature

can be a selective factor for individuals with optimal immune gene repertoires. These examples suggest that fish exposed to heat stress are restrained in their immuno-competence, which facilitates infections and increases selective pressure on fish immunity.

Further evidence comes from laboratory infections of sticklebacks with a parasitic tapeworm (*Schistocephalus solidus*). The tapeworm parasitizes three-spined sticklebacks as specific second intermediate hosts and develops in their body cavities. Final hosts are warm-blooded animals such as fish-eating birds (Dubinina, 1957; Smyth, 1946). Immune responses of laboratory-infected sticklebacks against the parasite, such as the amount of head kidney leukocytes and their respiratory burst activity, were much higher at relatively low (9°C to 15°C) temperatures and associated with supressed parasite growth. At higher temperatures lower leukocyte activity coincided with much faster growth of the parasite (Figure 2) (Franke *et al.*, 2017; Franke *et al.*, 2019; Scharsack *et al.*, 2021). For this parasite, higher body weight correlates with higher numbers of offspring, and thus immune suppression of its host at warm temperatures provides fitness benefits to the parasite.

The examples from cod and stickleback, indeed, suggest that teleost immunity is compromised at rising temperatures and that parasites may gain fitness under warmer conditions. To date, only a limited number of parasite (pathogen) species have been investigated in teleosts at high temperatures. Although some parasites, such as *S. solidus*, benefit from a mismatch of the host's and the parasite's temperature optima, other pathogens that match with their hosts' temperature optimum might not benefit from rising temperature. Taken together, tolerable temperatures above the optimal temperature range seem to coincide with the reduced efficiency of the teleost immune system. Accordingly, increasing temperature might promote pathogen reproduction and the spread of infectious diseases among teleosts. Nonetheless, the underlying mechanisms have hardly been investigated yet, a gap that awaits to be closed in the face of global warming.

5 | TEMPERATURE SHIFTS

In aquaculture systems, as well as in the wild, teleosts are exposed to "natural" temperature variation. The amplitude of the variation may vary between a few degrees in closed aquaculture systems or in habitats near the equator over seasonal variation, *e.g.*, in shallow lakes in the temperate climate zones to considerable daily variation, *e.g.*, in ponds or tidal estuaries. Accordingly, fish species adapted to different latitudes and habitat types differ in their tolerance to temperature shifts.

5.1 | Effects of temperature shifts on teleost immunity

The maintenance of cell membrane fluidity is an important factor for the susceptibility of teleost immunity to rapid temperature shifts. It was demonstrated in channel catfish that the composition of saturated and unsaturated fatty acids in the cell membrane is adjusted to keep membrane fluidity within a specific temperature range (Bly *et al.*, 1986). When temperature changes, the composition of membrane fatty acids needs to be readjusted, which takes time (Bly *et al.*, 1986). Meanwhile, the aggregation of immune receptors at cellular poles ("capping") is disturbed and receptor-mediated immune responses are impaired (Bly *et al.*, 1986). This explains why common carp, upon immunisation at 20°C and a temperature shift to 12°C after 8 days, did not show an antibody response, whereas those shifted after 15 days did (Avtalion, 1969).

Rapid upward temperature shifts, as well, impact fish immunity negatively. Phagocytes isolated from 13°C adapted sticklebacks and shifted to 24°C *in vitro* lost their responsiveness to stimulation with an antigen (zymosan), suggesting that thermal stress erased their responsiveness to immune stimulation. By contrast, phagocytes from warm-adapted sticklebacks (24°C) responded to *in vitro* stimulation with zymosan at 24°C, suggesting that previous adaptation to high temperature retains responsiveness to immune stimulation (Scharsack *et al.*, 2016). Similar observations were made with Japanese medaka (*Oryzias latipes*) after temperature shifts from 25°C to 30°C (Prophete *et al.*, 2006). These findings illustrate that temperature shifts have direct effects on teleost cellular immune functions.

5.2 | Temperature shifts induce stress

The level of stress induced by a temperature shift depends on several factors, which makes it extremely difficult to investigate and understand responses of teleost immunity to temperature shifts. These factors include the natural temperature range of the teleost species of interest, the acclimatisation temperature within this range, the amplitude and the speed of the temperature shift (Cheng *et al.*, 2009; Dittmar *et al.*, 2014; Makrinos & Bowden, 2016; Perez-Casanova *et al.*, 2008). Generally, temperature shifts, both up and down, are stressful for teleosts, in particular if temperature changes rapidly (Cheng *et al.*, 2009; Le Morvan-Rocher *et al.*, 1995).

Although it is well established that temperature shifts induce stress in fish, it is not well understood how this interferes with fish immunity. It was suggested that interactions between thermal effects and temperature-induced stress influence immune functions in Atlantic cod exposed to a chronic temperature increase of 1°C every 5 days from 10°C to 19°C (Perez-Casanova *et al.*, 2008). In this study, fluctuations in plasma cortisol levels corresponded to patterns of immune gene expression, suggesting interactions between the stress axis and immune traits. Thermal stress coincides with cell and tissue damage, which may also interfere with immune activity.

In three-spined sticklebacks, swollen spleens were observed after experimental exposure to a heat wave without pathogenic challenge. The authors suggested that cell and tissue damage was the causative factor for the swelling of spleens when cellular debris was cleared from the blood stream (Dittmar *et al.*, 2014). Another study proposed that cell and tissue damage induced by thermal stress caused inflammatory responses in livers in black rockfish (*Sebastes schlegelii*) after shifting temperatures from 16°C to either 5°C or 27°C (Lyu *et al.*, 2018). Taken together, these studies suggest that teleost

immunity is affected by temperature shifts indirectly, due to stress responses (*e.g.*, cortisol levels) and responses to cell and tissue damage.

5.3 | Long-term effects of temperature shifts

The possibility that temperature shifts can have long-term effects on teleost immunity is supported only by few studies yet. It was observed in stickleback that alterations in immune traits by temperature change could last relatively long if temperature was returned to the permissive range. The respiratory burst response of stickleback leukocytes as well as the lymphocyte proliferation rate were still elevated after 2 weeks at control temperature after an experimental heat wave (Dittmar *et al.*, 2014). A further example for long-lasting temperature effects – even beyond developmental stages – is given by Mateus *et al.* (2017). They found that thermal imprinting was present in adult sea bream (*S. aurata*) after their exposure as larvae to high (22°C), low (18°C) and shifts between the two temperatures. Sea bream that were exposed to high temperature or shifts from the low to the high temperature as larvae exhibited reduced responsiveness of innate immune traits when exposed to confinement stress as adults. This suggests that exposure to temperature shifts early in life can have effects on the stress responsiveness in later developmental stages.

5.4 | Temperature shifts and pathogens

When temperature shifts coincide with pathogen infections, effects on teleost immunity become more complex. Spleen transcriptome responses of Atlantic cod were only slightly affected by a moderate temperature increase, but showed prominent changes when the fish were additionally stimulated by intraperitoneal injections with viral antigens (Hori *et al.*, 2012). These experiments illustrate that fish leukocytes are susceptible to temperatures shifting upwards. Nonetheless, temperature drops may also cause immunological disorders in fish. In channel catfish aquaculture, rapid temperature drops (in the range of 10°C/24 h) led to a disease termed "winter saprolegniosis" or "winter kill." Saprolegnia is an opportunistic fungal pathogen, which is generally controlled by competent piscine immunity. Upon cold snaps, catfish were immunocompromised and lost their ability to control the pathogen (Bly *et al.*, 1992; Bly *et al.*, 1993; Bly & Clem, 1991).

There is no doubt that rapid temperature shifts (up and down) are stressful to teleosts. The faster a temperature change proceeds, the steeper its ramp and the bigger its amplitude, the more stress it will induce. Accordingly, for investigating effects of temperature shifts on fish immunity, it is essential to standardise parameters of temperature shifts, including the acclimation time before a temperature shift is induced. Detailed information on experimental temperature profiles should be included in scientific publications, to enable the reader to estimate the stress level of experimental individuals that might have affected scientific outputs.

Taken together, temperature shifts have direct and indirect effects on teleost immunity. The physiology of immune cells is directly affected by temperature shifts, and they may lose their responsiveness to antigen stimulation during the phase of readjustment to a changed temperature regime. Indirectly, thermal stress activates the neuronal stress axis, which alters the expression of immune traits. In addition, cell and tissue damage, coinciding with thermal stress, may trigger proinflammatory processes and activate immune traits involved in the clearance of immune complexes and cellular debris. Temperature shifts challenge the teleost immune system on multiple levels, and it might be diverted and seems to reduce or even lose responsiveness to additional stressors, including infections.

6 | LOCAL ADAPTATION TO TEMPERATURE REGIMES

Teleost species live in various habitats that differ substantially in their temperature conditions (Wootton, 1999). Within species, teleosts colonise habitats with different temperatures and tend to develop local adaptation to temperature regimes (Case *et al.*, 2005; Schulte, 2001; Schulte, 2013). This suggests that susceptibility of an individual fish population to temperature variation is influenced by its local adaptation; in other words, ecotypes adapted to warmer condition or more frequent temperature shifts might be more robust under climate change conditions.

As an example, a regional strain of rainbow trout, the so-called BORN trout, developed relatively high robustness against thermal stress. The strain was adapted for several decades to aquaculture conditions of a lagoon with huge temperature variation in the Baltic Sea. With a common garden experiment, offspring from the BORN strain and offspring reimported from the area of origin in North America were exposed to high (23°C) and low (8°C) temperatures. The BORN trout showed lower stress responses to temperature change compared to the reimported rainbow trout (Verleih *et al.*, 2015). Nonetheless, this study did not reveal prominent differences in the immune gene expression response to moderate cold and heat stress.

In three-spined sticklebacks, the expression response of immune candidate genes (Il1, TNF, TGF, MHC II, IgM) in spleens to an experimental heat wave was dependent on the temperature regime the sticklebacks originated from. Sticklebacks from a brook that were rather cold-adapted responded with higher upregulation of immune genes to a heat wave, whereas sticklebacks originating from a pond, with higher temperature variation, showed lower gene expression responses to the heat wave (Dittmar *et al.*, 2014). This shows that fish indeed adapt and adjust to local temperature regimes and that such adaptations influence interactions between immunity and temperature variation.

It was also investigated if local temperature adaptations interfere with immune responses to pathogens. Sticklebacks originating from a warm spring-fed site in the Icelandic lake Mývatn had lower leukocyte responses to infection with the tapeworm *S. solidus* compared to conspecifics from a cold site in the same lake (Franke *et al.*, 2017).

Differences between stickleback origins were evident only in combination with parasite infection, and sham-infected control fish from the two origins did not differ in their leukocyte response at different temperatures (13 *vs.* 24°C). Thus, local temperature adaptation within species seems to play a role with respect to temperature-mediated immuno-modulation but becomes obvious only upon pathogenic challenges. Schade *et al.* (2014) exposed three-spined sticklebacks from three different marine origins to 17°C and 21°C and bacterial infection (*Vibrio sp.*). They found that sticklebacks grew faster and were less susceptible to infection at 17°C. Both growth performance and disease susceptibility differed across the three origins.

These observations show that teleosts adapt to their local temperature regimes and that such local adaptation interferes with responses to pathogenic challenge. These examples highlight the high adaptability of teleosts to environmental conditions, which might facilitate adaptations to future climate change–induced variation in temperature regimes. A critical question to this end will be how fast environmental changes will develop and with which levels of variation they coincide. Rapid changes with huge temperature shifts will likely have strong negative effects on teleost immunity and may be associated with fitness losses of fish populations. Moderately increasing temperatures and not too extreme shifts, on the contrary, might not have negative effects given the adaptive potentials of teleosts.

7 | SEASONAL VARIATION OF IMMUNITY

In the temperate zone, teleosts are naturally exposed to temperature changes during seasonal cycles. Parasite infections show seasonal variation too and were most abundant at warm temperatures (Lugert *et al.*, 2017; Schade *et al.*, 2016). Accordingly, it is expected that teleost immune activity varies with seasons. Indeed, haematological and innate immune parameters of sea bass (*Dicentrarchus labrax*) in semi-intensive aquaculture were generally higher in summer, than in winter (Pascoli *et al.*, 2011). This coincides with observations that teleost immune activity increases with temperature. During winter, innate humoral immunity of sea bass remains active and responsive, which did not only depend on temperature, but also on the photoperiod (Valero *et al.*, 2014).

Year-long profiling of immune gene expression from wild-caught sticklebacks revealed prominent seasonal variation. As expected, signatures of adaptive immunity were elevated in late summer. In contrast, in late winter signatures of innate immunity (including IL-1 signalling and non-classical complement activity) and modulated toll-like receptor signalling were upregulated. Negative regulators of T-cell activity were prominent among winter-biased genes, suggesting that adaptive immunity is actively downregulated during winter rather than passively following ambient temperature (Brown *et al.*, 2016).

Another long-term study monitored sticklebacks from the wild in comparison with heated mesocosms and laboratory experiments with natural and accelerated (2 × within 24 h) photoperiodic change at 7°C and 15°C. The laboratory experiment demonstrated that immune allocation was independent of photoperiod. On the contrary, experimentally determined thermal effects predicted much of the summer-winter fluctuation observed in the field and mesocosms. Nonetheless, temperature was insufficient to fully predict natural patterns and thus can be overridden by other (unidentified) natural environmental variation (Stewart *et al.*, 2018b).

Combining temperature treatments with parasite infections is an interesting approach to investigate the effect of (seasonal) temperature variation on teleost immunocompetence in controlled laboratory experiments. Long-term investigations, *e.g.*, with three-spined sticklebacks in heated mesocosms (2°C above ambient) in comparison with laboratory temperature exposures suggest rather complex interactions of disease development and host immunity. In this experiment infection success of the parasitic hookworm (*Gyrodactylus gasterostei*) was higher and peaked later when parasite exposure was performed at low temperatures, supporting that acquired immunity is less efficient in the cold. Expression of candidate immune genes (T- and B-cell markers) was warm biased in response to the prevailing temperature but cold biased in response to temperature shifts (Stewart *et al.*, 2018a).

In sum, these observations clearly demonstrate seasonality of both, immunity and parasite infections of teleosts, whereby seasonal changes in immune activity match with requirements to defend the seasonal infection pressure. Infection pressure generally increases with temperature and is often highest in summer. Accordingly, high activity of the teleost immune system in the warm season is adaptive. Nonetheless, maintenance of immune activity is costly, and it should be downregulated, when infection pressure decreases.

7.1 | Winter suppression of immunity

Generally, teleost immune activity is downregulated in winter, at low temperature with the acquired immune system being less responsive. Accordingly, vaccination of fish in winter is not practical. Temperature alone does not seem to be the exclusive driver of downregulated immunity during winter in many teleosts, because Arctic fish species are able to maintain acquired immunity at very low temperatures. In the wild, infection pressure is higher during warm periods (Lugert *et al.*, 2017; Schade *et al.*, 2016) and factors such as photoperiod, nutrition, age and reproductive status are influential as well (Bowden *et al.*, 2007; Richard *et al.*, 2016). Immune suppression of teleosts from temperate climate zones during winter might also be an adaptation to save energy during the cold season. Nonetheless, the fact that immune activity of fish undergoes seasonal variation has important implications for fish health management in the wild and in aquaculture, but also for the conduction of immunological experiments under laboratory conditions.

In gilthead seabream (*S. aurata*) aquaculture in the northern Mediterranean, a phenomenon called "winter syndrome" causes huge economical losses due to growth depression and mortalities caused by opportunistic pathogens (Ibarz *et al.*, 2010). "Winter syndrome" coincides with downregulation of innate and acquired immunity in sea bream (Contessi *et al.*, 2006; Tort *et al.*, 1998a). Nonetheless, the usage of "winter food" with extra supplement of vitamins C, D and E and marine protein sources reduced immune suppression at cold temperatures and mitigated the symptoms of "winter syndrome"

(Richard *et al.*, 2016; Schrama *et al.*, 2017; Tort *et al.*, 2004). This supports the assumption that not low temperature alone results in seasonal immunosuppression in teleosts. This is in line with observations that immunity and metabolism are closely connected in vertebrates (Wang *et al.*, 2019), including teleosts (Pereiro *et al.*, 2019; Scharsack *et al.*, 2021).

The driver of seasonal changes in the immune activity of teleost might be the necessity to optimise the allocation of resources. High immune activity pays off in summer, when it is capable of defending pathology and nutrient drain caused by pathogens. When activity of pathogens slows down with temperature over winter, it is more cost efficient to downregulate expensive traits such as immunity.

8 | ADAPTIVE CAPACITY OF TELEOSTS TO CLIMATE CHANGE

Climate change will influence many environmental variables in aquatic habitats. In freshwater habitats, changes in precipitation and draughts and in the oceans alterations in salinity and acidity might become similarly important for teleosts as changes in temperature regimes. Importantly for teleost immunity, climate change will often alter several environmental factors contemporarily which might become more stressful to teleosts than changes in a single factor. Teleosts will also be exposed to indirect effects of climate change, such as changes in food availability.

On a macroevolutionary scale, teleosts have evolved adaptations to almost all aquatic environments on earth, and within each habitat are able to tolerate temperature variation, at least to some degree. The frame of temperature adaptations of teleosts is given by the climate region inhabited. Currently, geographic changes in climate regions are ongoing; for example, temperate climate zones are spreading towards the poles and polar regions are shrinking. Teleosts follow such geographic changes in climate zones and shift their distribution areas; for example, European sea bass (*D. labrax*) (Cardoso *et al.*, 2014) and Atlantic cod (*G. morhua*) (Engelhard *et al.*, 2014) are shifting north. Such changes in distribution areas compensate the necessity to adapt to changed temperature regimes.

From an evolutionary perspective on teleost immunity, in the light of climate change, a central question is, to which degree the evolutionary capacity of teleosts will succeed to adapt to changing environments? Large-scale adaptations, in the magnitude of a shift between climate zones (*e.g.*, from polar to temperate), are unlikely to occur at the same speed as climate change is progressing. Nonetheless, teleosts are also endowed with evolutionary capacities, which facilitate relatively fast adaptations, such as local adaptations to habitats that differ in temperature regimes.

8.1 | Local adaptation to temperature

The three-spined sticklebacks (*G. aculeatus*) is well known for its adaptions to different aquatic habitats ranging from marine to fresh water (Wootton, 1984). After the last deglaciation, approximately 10,000 years ago, sticklebacks have recolonised freshwater habitats from marine ancestors and have formed distinct ecotypes (Baker *et al.*, 2005; Eizaguirre *et al.*, 2011; Raeymaekers *et al.*, 2010; Reusch *et al.*, 2001; Scharsack *et al.*, 2007). Different stickleback origins also show immunological adaptations to distinct temperature regimes, such as warm and cold sites of a volcanic Icelandic lake (Franke *et al.*, 2017; Karvonen *et al.*, 2013), pond and brook temperature conditions (Dittmar *et al.*, 2014) and marine estuaries (Schade *et al.*, 2014). Such temperature adaptations of sticklebacks might have evolved since the last deglaciation, so on a scale of thousands of years/generations. Nonetheless, the example of rainbow trout adapted to higher robustness to thermal stress during *c.* 50 years rearing in a brackish lagoon in the Baltic Sea (Verleih *et al.*, 2015) suggests that temperature adaptations are also possible within decades.

8.2 | Epigenetics can facilitate rapid temperature adaptation

The relative importance of genetic *vs.* epigenetic changes in adaptive evolution is an intensely debated topic. More and more studies illustrate that some species adapt rapidly to environmental change without significant genetic change. The underlying epigenetic mechanisms are not fully understood yet. The methylation of DNA seems to encode gene expression profiles that were frequently used lifelong, and such information is transferred to the next generation. Exposure of eggs from Atlantic salmon (*S. salar*) to different temperatures (4 *vs.* 8°C) resulted in faster growth until harvest of the 8°C group, which was associated with high larval myogenin expression and low DNA methylation patterns (Burgerhout *et al.*, 2017).

A study on cartilagous fish, the winter skate (*Leucoraja ocellata*), observed that an endemic population was able to adapt to a 10°C higher water temperature over short evolutionary time (7000 years). The authors observed that the adaptive response to selection has an epigenetic basis in gene expression that may have enabled this species to rapidly respond to the novel environment. The endemic skate reduced its body size by 45%, below the minimum maturation size of other populations of winter skate, as well as exhibited other adaptations in life history and physiology (Lighten *et al.*, 2016).

Studies on epigenetics effects in teleosts are sparse, but first evidence indicates that temperature adaptation of teleosts is indeed mediated by epigenetic mechanism. This means that responses to changing temperatures during the lifespan of one generation enable the transfer of information to the next generation. In a climate change scenario, epigenetic mechanisms might therefore facilitate adaptations to changing temperature regimes. Our understanding of epigenetic mechanisms and its possible limitations is still in its infancy. Nonetheless, a possible perspective might be that epigenetic modifications will facilitate adaptations of fish to moderate changes in temperature regimes.

8.3 | Transgenerational plasticity and cryptic genetic variation

Transgenerational plasticity, by which parental environments shape offspring phenotypes, has been proposed as an alternative way to

respond to environmental changes (Pigliucci & Muller, 2010). As an example, exposure of sticklebacks to 17°C and 21°C of one generation (*c.* 1 year) resulted in distinct phenotypes, which were still present in their offspring [21°C sticklebacks had lower growth capacity (Shama *et al.*, 2014)]. This temperature adaptation was even transferred to the third stickleback generation (Shama *et al.*, 2016; Shama & Wegner, 2014). The mechanisms underlying such transgenerational plasticity are not fully understood yet, but it has been described that sticklebacks are endowed with the epigenetic toolkit to modulate such adaptations (Fellous & Shama, 2019).

Cryptic genetic variation uses genetic information that is implemented in the genome, but not expressed under the given environmental conditions. When the environment changes, cryptic genetic variation is released which increases the phenotypic variation that is subjected to selection (under the "new" environmental conditions). Accordingly, cryptic genetic variation can also explain fast responses to environmental change (Paaby & Rockman, 2014). For example, fast-growing marine three-spined sticklebacks expressed more slow-growing freshwater phenotypes within one generation upon transfer to low salinity (McGuigan *et al.*, 2011). Similarly, stickleback females exposed to constantly high and fluctuating temperature conditions adjusted egg size and released cryptic genetic variation in the offspring to adjust their growth performance in relation to the temperature regimes the mothers were exposed to (Shama, 2017). Information on cryptic genetic variation in immunological processes is sparse. It was suggested to use T-cell receptor diversity as a model to study cryptic genetic variation, because T-lymphocytes change and adjust their receptor repertoire in response to the pathogenic environment a host is exposed to during its life span (Whitacre *et al.*, 2012).

Taken together, first evidence on growth performance suggests that epigenetic effects and cryptic genetic variation may facilitate adaptation of teleosts to changing temperature regimes. Nonetheless, information on whether immunological temperature adaptation is mediated by epigenetics and cryptic genetic variation is, to the best of the author's knowledge, not available to date. Nevertheless, epigenetics and cryptic genetic information is limited and has presumably evolved as a mechanism to respond to "natural" environmental variation a species is exposed to. This may cover habitat-specific temperature extremes and thus support adaptation to changing thermal regimes, but will not enable adaptations to temperature shifts in the magnitude of climate zones.

9 | HOST–PATHOGEN CO-EVOLUTION IN A CHANGING CLIMATE

The strongest evolutionary pressure on fish immunity comes from the pathogenic "environment," which will be modified by climate change as well. Due to relatively short lifecycles, most pathogens/parasites adapt relatively faster to changing environmental conditions than their hosts. Indeed many authors suggest that parasites (evolutionary-biology defines "parasites" as "organisms that reduce the fitness of their hosts," which includes fungi, bacteria and viruses) will accelerate their lifecycle completion rates and the threat they pose to their hosts due to climate change (Hakalahti *et al.*, 2006; Hance *et al.*, 2007; Hoberg & Brooks, 2015; Lohmus & Bjorklund, 2015; Morley & Lewis, 2014; Poulin, 2007). Nonetheless, experimental evidence confirming such expectations is sparse. Indeed, a macro-parasite, the tapeworm *S. solidus* parasitizing sticklebacks, benefits under warmer conditions (Franke *et al.*, 2019). On the contrary, some fish viruses like the SPV of carp and the VHSV of salmonids are most active at relatively low temperatures, and their virulence might decrease when temperatures increase.

The complexity of climate change effects on pathogens is addressed in a number of excellent reviews (Altizer *et al.*, 2013; Barber *et al.*, 2016; Brooks & Hoberg, 2007; Cable *et al.*, 2017; Cohen *et al.*, 2017; Hance *et al.*, 2007; Marcogliese, 2008; Patz *et al.*, 2000; Raffel *et al.*, 2013). From the present knowledge, it is difficult to make predictions if climate change will be beneficial or detrimental to immunity and health of teleosts, as many variables are involved. A possible prediction is that climate change will affect teleost species and their pathogens differentially. Under certain circumstances, in particular if teleosts are subjected to temperature stress, pathogens will benefit from immunocompromised hosts. On the contrary, hosts will benefit if pathogens are specialised to certain temperature conditions, which become less abundant due to climate change.

Many climate change effects on host–pathogen interactions will be mediated indirectly through environmental change, such as humidity, shifts in the availability of food/prey or the abundance of intermediate hosts. Temperature and environmental changes, together, will reshape landscapes of host–pathogen interactions. Pathogens generally adapt faster to changing conditions due to their shorter generation times, and thus might at first take advantage from climate change. Nonetheless, pathogens depend on their hosts, and host overexploitation is a dead end for them. Hosts, on the contrary, are adapted to maintain immuno-competence under varying environmental conditions and might expand their adaptive range relatively fast. Accordingly, climate change is likely to accelerate the evolutionary arms race of hosts and pathogens.

10 | OUTLOOK

Acting in concert with pathogenic challenge, temperature variation can cause serious damage to fish stocks. The main temperature-related factors affecting host–pathogen interactions are (a) the adaptive/permissive range of fish host and pathogen, (b) the acclimatisation temperature of both as well as (c) the amplitude and (d) the speed (ramp) of temperature shifts. Although moderate changes in temperature, as they occur in nature, might be well received by the hosts (and pathogens), prominent temperature shifts may cause stress and long-lasting immunological disorders and may provide advantages to pathogens.

Past and present fish immunological research on temperature variation is complicated by the huge diversity of teleost species investigated, with their adaptations to many different temperature regimes

(22 species are referred to with the present review, Table 1). This makes it very difficult to standardise and summarise empirical evidences. A given temperature shift of, *e.g.*, 4°C per day might be harmless for some teleost families (like cyprinids and many percids) but can causes severe disorders in others (like Gadids and Salmonids).

Future research on temperature effects on teleost immunity might improve the standardisation of temperature protocols and provide information about the permissive temperature range of the species investigated. Ideally, the livelong temperature regime experimental fish were exposed to, including acclimation time and temperature prior to experiments, is presented in each publication. If experimental fish (or their cells) are subjected to temperature shifts, authors might provide and discuss available evidence to which extent the shift was stressful. Many studies provide such information, but making this a common sense in fish immunology research would help to gain deeper insight into teleost responses to temperature change.

In sum, some overarching patterns can clearly be identified. At cold temperatures, acquired immunity is supressed in many teleosts and their immuno-competence depends on innate immune traits. In the species-specific intermediate, permissive temperature range, immunity functions optimally and both innate and acquired immunity act against pathogens.

Rapid temperature shifts, up and down, cause stress and immunological disorders. Long-term exposure to high temperatures seems to be detrimental to teleost immune functions as well. Although short (temporal) exposure to temperature shifts can be tolerated by teleosts, if they can return to their preferred temperature, chronical exposure to temperature stress is detrimental to physiological and immune traits.

Due to climate change, temperature extremes and temperature shifts will occur more frequently. Therefore, complementation of the current knowledge on temperature effects on fish immunity is of high relevance for future management of wild and aquaculture fish stocks, facing the impact of global warming. Future research may help to close the gap in knowledge on effects of temporal and chronical exposure to temperature stress at the upper tolerable range of the species of interest.

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