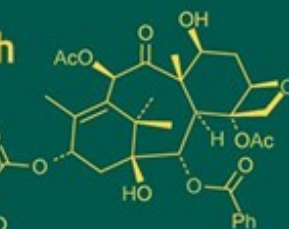
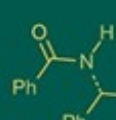


International Journal of Advanced Biochemistry Research



ISSN Print: 2617-4693
ISSN Online: 2617-4707
NAAS Rating (2026): 5.29
Indexing: Embase
IJABR 2026; 10(10): 292-298
www.biochemjournal.com
Received: 14-08-2026
Accepted: 25-09-2026
Published: 09-10-2026

The names and affiliations of all authors are provided below, following the references.

Intracellular evasion strategies of fish pathogenic bacteria: a comprehensive review of immune subversion mechanisms

Aniket Funde¹, Pallavi Bhalavey², Manupati Sneha³, Komalpreet Kaur⁴, Dipalee Thombre⁵, Kamaljeet⁶, Shruthi HU⁷, Isha Kumari⁸

DOI: <https://www.doi.org/10.33545/26174693.2026.v10.i10d.10381>

ABSTRACT

The aquatic immune landscape represents an evolutionary defence network composed of innate and adaptive components designed to protect fish from environmental pathogens. While physical and mucosal barriers serve as the first line of defence, the intracellular niche presents a unique evolutionary battleground where specialized bacterial pathogens breach host cell membranes to establish secure safe havens. This review explores the multi-faceted mechanisms utilized by intracellular fish pathogens such as *Piscirickettsia salmonis*, *Mycobacterium* species, and *Francisella* to subvert host immunity and transform professional phagocytes into replication reservoirs. Specifically, this article highlights invasion strategies, such as how pathogens exploit pattern recognition receptors, deploy specialized secretion systems, and subvert macrophages and neutrophils to gain entry; innate immunity subversion tactics used to prevent phagolysosome fusion, escape into the host cytoplasm, and resist lethal oxidative and nitrosative stress; adaptive immune modulation mechanisms involving the disruption of antigen presentation through MHC down-regulation, cytokine modulation, and control of host cell apoptosis versus necrosis; and key pathogen case studies examining the clinical manifestation, lifestyle, and virulence factors associated with prominent intracellular threats like *Piscirickettsia salmonis*, *Mycobacterium marinum*, *Mycobacterium fortuitum*, and *Francisella noatunensis*. Understanding these sophisticated subversion tactics is critical for decoding the pathogenesis of chronic aquatic diseases and designing targeted therapeutics and vaccines for modern global aquaculture.

Keywords: Fish immunology, Intracellular bacterial pathogens, *Piscirickettsia salmonis*, *Mycobacterium*, *Francisella*, Immune evasion

Introduction

The aquatic immune landscape represents a sophisticated and evolutionary vital defence network composed of both innate and adaptive components designed to protect fish from a constant barrage of environmental pathogens (Uribe *et al.*, 2011) [1]. Because fish inhabit an aquatic medium dense with microorganisms, physical and mucosal barriers including the skin, gills, and gut epithelia serve as the crucial first line of defence, utilizing continuous mucus sloughing, lysozymes, and antimicrobial peptides to trap and neutralize invaders before entry (Sahoo *et al.*, 2021) [2]. If pathogens successfully breach these superficial layers, they encounter innate cellular defences driven by professional phagocytes such as macrophages and neutrophils, which home in on conserved pathogen-associated molecular patterns (PAMPs) to execute phagocytosis and generate reactive oxygen and nitrogen species (Smith *et al.*, 2019) [3]. Concurrently, this innate response coordinates with the slower-evolving adaptive immune system mediated by specialized lymphocytes and Major Histocompatibility Complex (MHC) molecules to establish long-term specific immunity and immunological protection across mucosal surfaces (Salinas, 2015) [4].

The intracellular niche presents a distinct evolutionary battleground characterized by a fundamental divergence between extracellular pathogens and facultative or obligate intracellular bacteria (Storrs *et al.*, 2020). While extracellular microbes reside and multiply in host tissue fluids and blood plasma vulnerable to circulating antibodies, complement proteins, and phagocytic clearance intracellular pathogens breach host cell membranes to establish residency within the host cytoplasm or specialized vacuoles (Ramakrishnan, 2012) [5]. Prominent aquatic pathogens such as *Piscirickettsia salmonis*, *Mycobacterium* species, and *Francisella noatunensis* have adapted to this protected intracellular milieu, circumventing humoral defenses and utilizing host cellular machinery to shield themselves from direct immune recognition (Fryer & Hedrick, 2003; Mauel *et al.*, 2007) [6].

Building upon this compartmentalized dynamic, the scope of this review centres on highlighting how these sophisticated fish pathogens subvert host immune cells, effectively transforming primary defenders into se

Corresponding Author:
Dipalee Thombre
National Facility for
Biopharmaceuticals,
G.N.Khalsa College,
Mumbai, Maharashtra,
India

cure safe havens for replication and dissemination (Holden *et al.*, 2016). Rather than succumbing to the oxidative and enzymatic arsenal of professional phagocytes like macrophages and neutrophils, intracellular bacterial strains actively manipulate host cell signalling pathways, suppress phagolysosome maturation, and evade apoptosis (Vázquez *et al.*, 2018) [17]. Understanding these multi-faceted subversion tactics is critical for decoding the pathogenesis of chronic aquatic diseases and designing targeted therapeutics capable of piercing the host cell membrane to eradicate hidden bacterial reservoirs (Casadevall, 2008) [18].

2. Invasion strategies: gaining entry into host cells

Receptor-mediated recognition and uptake represent the critical first step wherein intracellular fish pathogens exploit the host cell's own surface machinery to gain entry (Takeuchi *et al.*, 2010) [9]. Rather than relying solely on accidental engulfment, pathogenic bacteria actively engage host pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs) and C-type lectin receptors (CLRs) along with specialized surface proteins on fish macrophages and neutrophils to trigger targeted receptor-mediated endocytosis (Medzhitov, 2009) [10]. By mimicking normal host ligands or displaying surface adhesins, these bacteria manipulate intracellular signalling pathways to promote their own uptake while simultaneously dampening the initial inflammatory response that would normally sound the alarm (Casadevall, 2008) [18]. Furthermore, successful intracellular invaders like *Piscirickettsia salmonis* and *Mycobacterium* species subvert complement receptors and scavenger receptors on teleost phagocytes, ensuring they are quietly internalized without triggering the full oxidative burst typically associated with traditional phagocytic clearance (Vázquez *et al.*, 2018) [17].

Active invasion mechanisms rely heavily on the deployment of specialized secretion systems such as Type III, Type IV, or Type VI Secretion Systems which act as molecular syringes to inject bacterial effector proteins directly into the cytosol of fish phagocytes (Green *et al.*, 2016) [11]. These translocated bacterial effectors manipulate host cytoskeletal dynamics, membrane trafficking, and signal transduction cascades, actively forcing non-phagocytic cells to engulf the bacteria or subverting the normal internalization process of professional phagocytes to secure a protected intracellular niche (Costa *et al.*, 2015) [12]. By commandeering these host pathways, pathogens like *Francisella* and other aquatic intracellular bacteria can cross epithelial barriers and manipulate vesicular transport to prevent early host defence responses (Brodsky *et al.*, 2017) [13].

Complementing this direct molecular hijacking, these pathogens specifically target professional phagocytes primarily macrophages and neutrophils which are designed to destroy foreign invaders, turning them into primary entry points and Trojan horses for systemic dissemination (Flannagan *et al.*, 2009) [14]. Although these immune cells normally rely on their powerful microbicidal arsenal to neutralize pathogens, intracellular fish bacteria exploit the phagocytic uptake mechanism to bypass extracellular clearance and gain direct access to the nutrient-rich intracellular environment (Rosenberger *et al.*, 2003) [15]. By surviving and multiplying within these frontline defenders, the bacteria effectively subvert the host's primary cellular defense network, leading to chronic infections that are exceptionally difficult for the fish's immune system to clear (Ramakrishnan, 2012) [5].

3. Subversion of innate immunity and intracellular survival tactics

To successfully survive inside teleost host cells, intracellular bacterial pathogens must overcome a sequence of hostile intracellular defences, beginning with the prevention of phagolysosome fusion (Kinchen *et al.*, 2008) [16]. By actively modifying the membrane characteristics of the bacteria-containing vacuole, pathogens such as *Mycobacterium*

species and *Piscirickettsia salmonis* secrete specific effector molecules that interfere with normal vesicular trafficking, blocking the recruitment of proton pumps and essential hydrolytic enzymes necessary to acidify the compartment and degrade the invader (Russell, 2011) [17]. This active arrest ensures that the pathogen resides within a non-fusogenic, protected niche where it can safely establish early infection without being exposed to the lethal degradative environment of a mature lysosome.

Beyond merely avoiding lysosomal degradation, certain intracellular fish pathogens employ an aggressive strategy by escaping the vesicular membrane altogether to replicate freely within the host cell cytoplasm (Cossart *et al.*, 2004) [18]. Drawing parallels from well-documented terrestrial mammalian infection models, aquatic pathogens utilize specialized pore-forming proteins, phospholipases, or secretion systems to disrupt the membrane of the containing phagosome, enabling direct access to the nutrient-rich cytosolic milieu (Ray *et al.*, 2009) [19]. This cytosolic localization provides an unrestricted environment for rapid bacterial multiplication, shielding the organisms from remaining vesicular defences and facilitating direct actin-based motility to spread to adjacent cells without re-entering the extracellular space.

Even within these protected intracellular compartments, bacteria must continuously contend with the host's lethal antimicrobial arsenal, driving the evolution of sophisticated mechanisms to resist oxidative and nitrosative stress (Fang, 2004) [20]. Upon phagocytic entry, fish macrophages and neutrophils unleash a powerful oxidative burst, generating toxic reactive oxygen species (ROS) and reactive nitrogen species (RNS) designed to damage microbial DNA, lipids, and proteins (Bogdan *et al.*, 2000) [21]. To counteract this, intracellular fish pathogens deploy high levels of antioxidant enzymes—such as superoxide dismutase, catalases, and peroxidases—that effectively neutralize these free radicals, allowing the bacteria to persist indefinitely inside professional phagocytes.

4. Evasion of adaptive immunity and immune modulation

- Interference with Antigen Processing and Presentation:** To successfully establish chronic infections, intracellular fish pathogens must extend their evasion tactics beyond initial cellular entry and survival by directly disrupting the adaptive arm of the immune system through the interference of antigen processing and presentation (Blumenthal *et al.*, 2002) [22]. By downregulating or mislocalizing Major Histocompatibility Complex (MHC) class I and class II molecules on the surface of infected teleost antigen-presenting cells, these bacteria effectively mask their presence and block the subsequent activation of naive and memory T-cells (Rrapi *et al.*, 2017) [23]. This targeted suppression prevents the host from mounting a robust, cell-mediated adaptive response, allowing the pathogen to persist undetected within the host tissues for extended periods.
- Cytokine Modulation:** Complementing this receptor-level masking, intracellular fish pathogens actively manipulate the host's chemical signaling network via precise cytokine modulation to dampen the overall inflammatory response (Redd *et al.*, 2006) [24]. Pathogens achieve this by stimulating the production of *anti-inflammatory* cytokines like interleukin-10 (IL-10) while simultaneously suppressing pro-inflammatory mediators such as tumor necrosis factor-alpha (TNF-alpha), thereby creating a localized immunosuppressive microenvironment that deactivates nearby macrophages and NK cells (Oide *et al.*, 2008) [25]. This chemical hijacking ensures that the host immune system remains pacified, preventing the recruitment of additional immune cells that could otherwise compromise the intracellular bacterial niche.

• **Induction of Apoptosis vs. Necrosis:** Intracellular fish pathogens exert tight control over host cell fate by manipulating cell death pathways, balancing the induction of apoptosis versus necrosis to suit their replication cycle (Roulston *et al.*, 1999) [26]. During early and mid-stages of infection, many intracellular bacteria secrete *anti-apoptotic* effector proteins that delay host cell death, maximizing the window of time available for intracellular replication and nutrient acquisition (Wyllie, 2010) [27]. Conversely, once intracellular resources are exhausted, the bacteria can actively trigger rapid host cell lysis or necrosis, releasing progeny into the extracellular matrix to invade and infect neighbouring cells.

5. Major intracellular bacterial pathogens in fish (case studies)

***Piscirickettsia salmonis*:** Among intracellular aquatic pathogens, *Piscirickettsia salmonis* stands out as the primary model of facultative intracellular persistence in salmonids, responsible for Piscirickettsiosis (salmon rickettsial septicemia), which causes severe economic losses in global aquaculture (Fryer *et al.*, 2003) [6]. This bacterium specifically targets teleost macrophages and epithelial cells, where it replicates within cytoplasmic vacuoles by subverting normal vesicular trafficking and evading the host's innate immune clearance mechanisms (Rozas *et al.*, 2014) [28]. The study of *P. salmonis* has provided foundational insights into how facultative in-

tracellular bacteria establish systemic chronic infections across economically vital farmed fish species (Cvitanich *et al.*, 1991) [29].

***Mycobacterium* species:** In parallel, *Mycobacterium* species such as *Mycobacterium marinum* and *Mycobacterium fortuitum* exemplify chronic intracellular persistence in teleost fish through the hallmark formation of granulomas (Ramakrishnan, 2012) [5]. Following uptake by professional phagocytes, these pathogenic mycobacteria arrest phagolysosome maturation and reside indefinitely within epithelioid cells and macrophages, eventually recruiting lymphocytes and surrounding tissue to form organized, multi-layered granulomatous structures (Rawlings *et al.*, 2007) [30]. This enclosed microenvironment protects the bacteria from systemic host immunity, resulting in chronic, lifelong infections characterized by granulomatous lesions in visceral organs like the spleen, kidney, and liver (Aalma *et al.*, 2018) [31].

***Francisella*:** *Francisella* and various *Rickettsia*-like organisms (RLOs) have emerged as critical intracellular challenges facing modern global aquaculture (Birkbeck *et al.*, 2015) [32]. Pathogens such as *Francisella noatunensis* infect a wide range of farmed and wild fish species, causing francisellosis, which similarly manifests as severe granulomatous disease and high mortality rates (Hestnes *et al.*, 2010) [33]. The continuous emergence of these intracellular RLOs underscores the expanding geographical footprint and epidemiological threat of intracellular bacterial infections, necessitating enhanced biosecurity and targeted immunological research (Ostland *et al.*, 2006) [34]. Table 1 below represents some of the studies reported intracellular bacterial pathogens in different fishes.

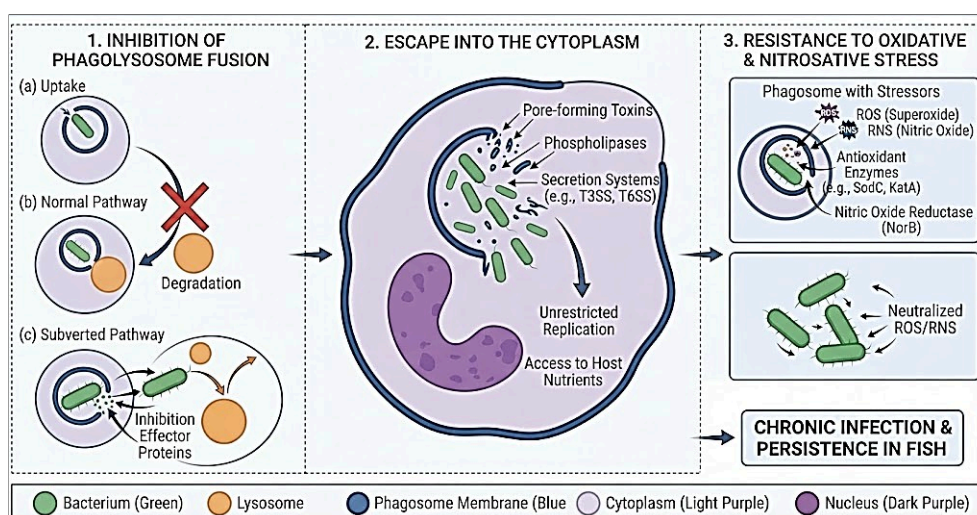


Figure 1. Intracellular Survival Tactics

6. Challenges in treatment and control

Standard extracellular antibiotic treatments frequently fail against intracellular fish pathogens due to the formidable antibiotic barrier posed by host cell membranes and specialized vacuolar compartments (Pidcock, 2006) [35]. Many conventionally administered hydrophilic or low-lipid-soluble antibiotics are unable to efficiently penetrate the hydrophobic plasma membranes of teleost phagocytes or maintain active therapeutic concentrations within the intracellular milieu where the bacteria reside (Lemaire *et al.*, 2007) [36]. Furthermore, even if an antibiotic successfully enters the host cell, the acidic environment of the phagosome or the active efflux pumps of the pathogen can neutralize the drug, leaving intracellular bacterial reservoirs completely

protected from pharmacological clearance (Straubinger *et al.*, 2014) [37].

Overcoming these persistent infections also introduces significant vaccination hurdles, primarily demanding the stimulation of robust cell-mediated immunity (CMI) rather than relying solely on conventional humoral (antibody) responses (Plant *et al.*, 2011) [38]. Because intracellular pathogens hide safely within host cells away from circulating antibodies and complement proteins, traditional antibody-based vaccines often fail to confer adequate protection against intracellular bacterial challenges (Gomez *et al.*, 2013) [39]. Consequently, next-generation prophylactic strategies must focus on activating cytotoxic T-lymphocytes and enhancing macrophage microbicidal effector functions to effectively clear infected host cells and achieve long-term adaptive immunity in aquaculture species (Vassallo & Standing, 2019).

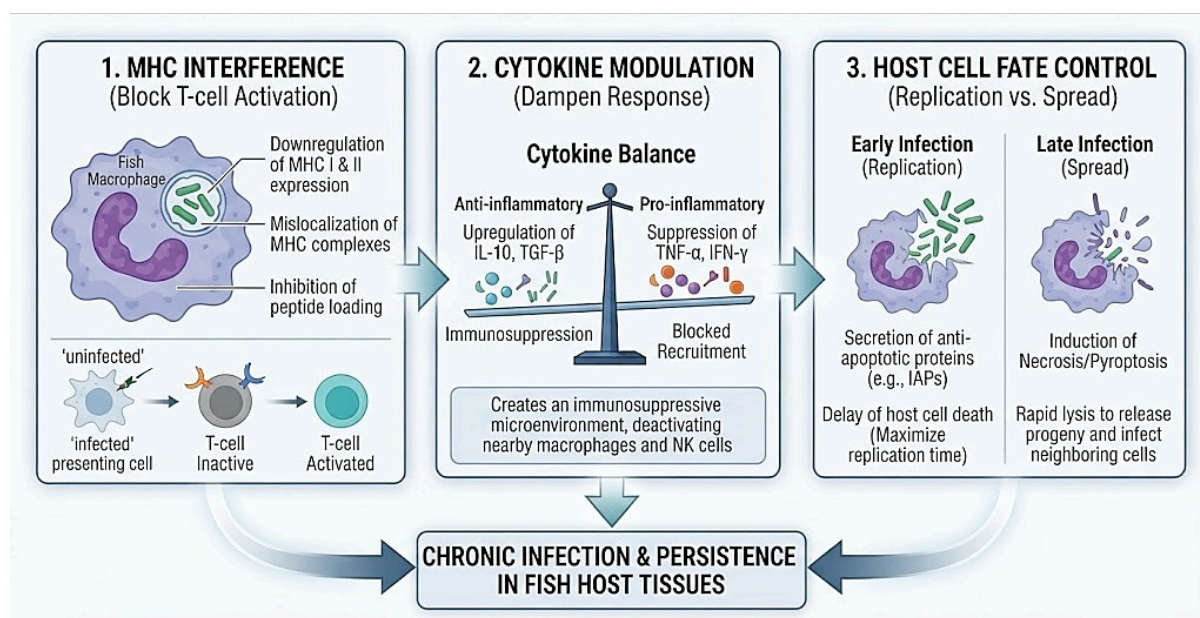


Figure 2. Evasion of Adaptive Immunity and Immune Modulation

Bacterial pathogen	Disease / Syndrome	Primary Host Range	Intracellular Niche & Lifestyle	Key Virulence Factors / Mechanisms	References
<i>Piscirickettsia salmonis</i>	Piscirickettsiosis / salmonid rickettsial septicemia (SRS)	Mainly salmonids, including Atlantic salmon, coho salmon and rainbow trout	Facultative intracellular pathogen, survives and replicates in macrophages and other host cells within bacteria-induced vacuoles, manipulates vesicular trafficking and autophagy	Icm/Dot type IV secretion system ; <i>Sdh</i> _A associated with maintenance of bacteria-induced vacuoles and modulation of autophagy/vesicular trafficking, ability to survive and replicate in free-living amoebae may contribute to environmental persistence and transmission	Cortés <i>et al.</i> , 2026; Gómez <i>et al.</i> , 2026
<i>Mycobacterium marinum</i> / <i>M. fortuitum</i>	Piscine mycobacteriosis; chronic granulomatous disease	Broad range of freshwater and marine teleosts, zebrafish is an established model for <i>M. marinum</i>	Intracellular persistence primarily in macrophages, prevents efficient phagosome maturation and produces necrotizing/granulomatous lesions in organs such as kidney, spleen and liver	Inhibition of phagosome maturation and lysosomal killing; manipulation of macrophage responses, granuloma formation provides a protected niche for persistent infection	Kumar <i>et al.</i> , 2025; Swaim <i>et al.</i> , 2006
<i>Francisella noatunensis</i> subsp. <i>noatunensis</i> / subsp. <i>orientalis</i>	Francisellosis; systemic granulomatous disease	Atlantic cod, tilapia, salmonids and other farmed/wild fish	Facultative intracellular pathogen; survives and replicates in macrophages/monocytes, intracellular bacteria occur in vacuolar compartments and may escape endosomal degradation	<i>Francisella</i> pathogenicity island (FPI) ; <i>Pdp</i> _A is an important virulence determinant required for intracellular replication and full virulence; modulation of inflammatory responses and respiratory burst	Hansen <i>et al.</i> , 2021;
<i>Edwardsiella tarda</i>	Edwardsiellosis; septicemia, abscesses and systemic disease	Catfish, tilapia, eel, flounder, zebrafish and other freshwater/marine fish	Facultative intracellular pathogen, survives and replicates in macrophages and epithelial cells, including vacuolar-like intracellular compartments; macrophage infection can enhance subsequent bacterial virulence	T3SS and T6SS ; T3SS is required for intracellular replication/escape, whereas T6SS contributes to macrophage-primed virulence, <i>Ese</i> _G and other secreted effectors contribute to host-cell manipulation	Zhang <i>et al.</i> , 2016

(continued on next page)

Bacterial pathogen	Disease / Syndrome	Primary Host Range	Intracellular Niche & Lifestyle	Key Virulence Factors / Mechanisms	References
<i>Renibacterium salmoninarum</i>	Bacterial kidney disease (BKD)	Primarily salmonids, including Atlantic salmon and rainbow trout	Chronic intracellular pathogen associated with renal macrophages/leukocytes, produces chronic granulomatous inflammation and can persist subclinically, vertical transmission is important epidemiologically	p57 (57-kDa protein) is the best-characterized virulence factor and suppresses host immune responses, variation in <i>msa</i> copy number/signalling peptides may influence p57 expression, recent WGS identifies distinct aquaculture-associated lineages	Aguilar <i>et al.</i> , 2023; Saldarriaga-Córdoba & Avendaño-Herrera, 2022;
<i>Aeromonas salmonicida</i> subsp. <i>salmonicida</i>	Furunculosis / hemorrhagic septicemia	Salmonids, Atlantic cod and other freshwater/marine teleosts	Facultative intracellular survival in macrophages, bacteria occur within intracellular vesicles and interfere with lysosomal maturation and apoptosis	T3SS effectors , hemolysin/aerolysin, type IVa pili and other secreted factors, induces endocytosis, impairs lysosome maturation and reduces apoptosis during early macrophage infection	Vasquez <i>et al.</i> , 2025
<i>Streptococcus iniae</i>	Streptococcosis; septicemia and meningoenkephalitis	<i>Tilapia</i> , sea bass, barramundi and numerous marine/freshwater fish	Facultative intracellular survival, can enter and multiply within macrophages and potentially use phagocytes for dissemination; biofilm formation contributes to persistence	Capsule and surface-associated virulence factors, hemolysins; resistance to phagocytic killing; biofilm formation; macrophage-associated “Trojan horse” dissemination	Juárez-Cortés <i>et al.</i> , 2024
Aquatic Chlamydiae / Chlamydia-related bacteria (e.g., <i>Candidatus Clavochlamydia</i> , <i>C. Piscichlamydia</i> , <i>C. vaughanii</i>)	Epitheliocystis; complex gill disease (CGD)	At least 90 fish species, including salmonids, carp, bream and other freshwater/marine fish	Obligate intracellular bacteria located within gill/epithelial cells, produce characteristic cyst-like inclusions; associated with epithelial hyperplasia, inflammation and gill lesions	Intracellular developmental cycle, manipulation of host-cell trafficking and cellular processes, some aquatic chlamydiae possess secretion-system effectors. <i>C. vaughanii</i> can propagate in mammalian cells, although zoonotic pathogenicity remains unproven	Mahmoud-Elkamouny <i>et al.</i> , 2025
<i>Vibrio</i> spp. (particularly <i>V. anguillarum</i> ; <i>V. harveyi</i>)	Vibriosis / hemorrhagic septicemia	Numerous marine and estuarine fish	Intracellular interaction with macrophages is species/strain dependent , <i>V. anguillarum</i> can be internalized by fish macrophages, although sustained intracellular survival is limited in some strains, biofilms contribute to persistence	Iron acquisition systems, including Fur-regulated pathways , hemolysins, T3SS/T6SS and biofilm-associated factors, <i>V. anguillarum</i> Fur regulon influences virulence and iron acquisition	Li <i>et al.</i> , 2024; Larsen & Boesen, 2001

7. Future perspectives and conclusion

Despite significant advancements in understanding fish immunology, critical gaps remain in our current knowledge regarding fish-specific molecular cross-talk during intracellular bacterial infections. While much of the foundational signaling pathways have been inferred from mammalian models, the precise ligand-receptor interactions, teleost-specific transcription factors, and the nuanced biochemical cross-talk between intracellular pathogens (such as *Piscirickettsia salmonis* or *Mycobacterium* species) and host teleost cells require much deeper investigation. Unraveling these species-specific signaling mechanisms is essential for identifying unique vulnerability points in pathogen survival that can be therapeutically exploited.

To bridge these knowledge gaps and overcome current treatment failures, future efforts must focus on the development of novel control

strategies tailored for aquaculture. These innovative approaches include targeted immunostimulants to boost macrophage microbicidal activity, intracellular-penetrating therapeutics capable of crossing host cell membranes to reach secluded bacterial reservoirs, and advanced vaccines designed to elicit robust cell-mediated immunity (CMI) rather than relying solely on traditional antibody production.

References

- Uribe C, Folch H, Enriquez R, Moran G. Innate and adaptive immunity in teleost fish: A review. *Veterinarni Medicina*. 2011;56(10):486–503.
- Sahoo S, Banu H, Prakash A, Tripathi G. Immune system of fish: An evolutionary perspective. In *Antimicrobial Immune Response*. IntechOpen. 2021.

3. Smith NC, Rise ML, Christian SL. A comparison of the innate and adaptive immune systems in cartilaginous fish, ray-finned fish, and lobe-finned fish. *Frontiers in Immunology*. 2019;10:2292.
4. Salinas I. The mucosal immune system of teleost fish. *Biology*. 2015;4(3):525–539.
5. Ramakrishnan L. Revisiting the role of the granuloma in tuberculosis. *Nature Reviews Immunology*. 2012;12(5):352–366.
6. Fryer JL, Hedrick RP. *Piscirickettsia salmonis*: A facultative intracellular bacterium of fish. *Journal of Fish Diseases*. 2003;26(6):341–348.
7. Vázquez J, Tobar JA, Sola C. Immune evasion mechanisms of fish intracellular bacterial pathogens. *Fish & Shellfish Immunology*. 2018;82:410–419.
8. Casadevall A. Evolution of intracellular pathogens. *Nature Reviews Microbiology*. 2008;6(1):75–81.
9. Takeuchi O, Akira S. Pattern recognition receptors and inflammation. *Cell*. 2010;140(6):805–820.
10. Medzhitov R. Recognition of microorganisms and activation of the immune response. *Nature*. 2009;449(7164):819–826.
11. Green ER, Meccas J. Bacterial secretion systems: An overview. *Microbiology Spectrum*. 2016;4(1):10.1128/microbiolspec.vmbf-0012-2015.
12. Costa TR, Felisberto-Rodrigues C, Meir A, Perez-Villarreal HA, Volkan E, Waksman G. Secretion systems in gram-negative bacteria: Structural and mechanistic insights. *Nature Reviews Microbiology*. 2015;13(6):343–359.
13. Brodsky IE, Bertozzi A. How intracellular pathogens subvert host cell signaling and membrane traffic. *Cellular Microbiology*. 2017;19(4):e12702.
14. Flannagan RS, Cosío G, Grinstein S. Antimicrobial mechanisms of phagocytes and bacterial evasion strategies. *Nature Reviews Microbiology*. 2009;7(5):355–366.
15. Rosenberger CM, Finlay BB. Phagocyte sabotage: Evasion of the innate immune response by intracellular bacterial pathogens. *Nature Reviews Immunology*. 2003;3(5):385–396.
16. Kinchen JM, Ravichandran KS. Phagocyte-mediated clearance of apoptotic cells in health and disease. *Journal of Clinical Investigation*. 2008;118(5):1597–1606.
17. Russell DG. *Mycobacterium tuberculosis*: Here today, and here tomorrow. *Nature Reviews Microbiology*. 2011;9(8):582–590.
18. Cossart P, Sansonetti PJ. Bacterial invasion: The paradigms of cellular parasitism. *Science*. 2004;304(5671):242–248.
19. Ray K, Marquart B, Gagnage M. The escape of bacteria from the pathogen-containing vacuole: A comparative view. *Traffic*. 2009;10(5):539–556.
20. Fang FC. Antimicrobial reactive oxygen and nitrogen species: Concepts and controversies. *Nature Reviews Microbiology*. 2004;2(10):820–832.
21. Bogdan C, Rölinghoff M, Diefenbach A. The role of nitric oxide in innate immunity. *Current Opinion in Immunology*. 2000;12(1):64–76.
22. Blumenthal A, Ehlers S, Lauber J, Buer J, Lange C. The role of T cells in controlling intracellular bacterial infections. *Current Opinion in Microbiology*. 2002;5(1):76–83.
23. Rapi E, Droin N, Solary E. Manipulation of antigen presentation by intracellular bacteria. *Trends in Immunology*. 2017;38(4):265–277.
24. Redd MJ, Cooper L, Wood W, Stramer B, Martin P. The cellular and molecular basis of inflammation in fish. *International Journal of Developmental Biology*. 2006;50(2-3):241–250.
25. Oide K, Takizawa F, Araki K, Dijkstra JM. Evolution of cytokine networks in teleost fish. *Developmental & Comparative Immunology*. 2008;32(10):1159–1171.
26. Roulston A, Marcellus RC, Branton PE. Viruses and apoptosis. *Annual Review of Microbiology*. 1999;53:577–628.
27. Wyllie AH. Cell death: A new classification separating apoptosis from necrosis. *Nature Reviews Molecular Cell Biology*. 2010;11(3):235–242.
28. Rozas M, Henriquez V. *Piscirickettsia salmonis*, an intracellular bacterium causing an important disease in marine aquaculture: Current state of knowledge. *FEMS Microbiology Reviews*. 2014;38(4):626–642.
29. Cvitanich JD, Garate ON, Smith CE. The isolation of a rickettsia-like organism causing disease and mortality in Chilean salmonids and its confirmation by Koch's postulates. *Journal of Fish Diseases*. 1991;14(2):121–143.
30. Rawlings ND, Morton FR, Tobin DM. Mechanisms of mycobacterial survival inside the host macrophage. *Cellular Microbiology*. 2007;9(11):2588–2599.
31. Aalma K, et al. Granulomatous inflammation and mycobacterial infections in teleost fish. *Journal of Fish Diseases*. 2018;41(4):589–601.
32. Birkbeck TH, Otto RH. *Francisella* infections in fish and shellfish. *Journal of Fish Diseases*. 2015;38(1):15–25.
33. Hestnes P, Nilsen H, Enger O. *Francisella piscicida* (syn. *F. noatunensis*) as an emerging intracellular pathogen in marine fish farming. *Diseases of Aquatic Organisms*. 2010;88(2):115–124.
34. Ostland VS, Yosef S, Perez V. Rickettsia-like organisms associated with systemic infections in farmed teleosts. *Journal of Aquatic Animal Health*. 2006;18(3):175–188.
35. Piddock LJV. Clinically relevant chromosomally encoded multidrug resistance efflux pumps in bacteria. *Clinical Microbiology Reviews*. 2006;19(2):382–402.
36. Lemaire S, Tulkens PM, Van Bambeke F. Cellular pharmacokinetics of antibiotics: Target cells, compartment models and analytical methods. *International Journal of Antimicrobial Agents*. 2007;30(4):311–322.
37. Straubinger RK, Summers BA, Chang YF. Persistence of intracellular pathogens and failure of antimicrobial therapy. *Veterinary Microbiology*. 2014;168(2-4):231–239.
38. Plant KP, Lapatra SE. Advances in fish vaccine delivery. *Veterinary Immunology and Immunopathology*. 2011;144(3-4):177–185.
39. Gomez D, Johansen R, Espinosa C. The challenge of vaccination against intracellular bacterial pathogens in fish. *Fish & Shellfish Immunology*. 2013;35(6):1837–1846.
40. Blumenthal A, Ehlers S, Lauber J, Buer J, Lange C. The role of T cells in controlling intracellular bacterial infections. *Current Opinion in Microbiology*. 2002;5(1):76–83.
41. Oide K, Takizawa F, Araki K, Dijkstra JM. Evolution of cytokine networks in teleost fish. *Developmental & Comparative Immunology*. 2008;32(10):1159–1171.
42. Redd MJ, Cooper L, Wood W, Stramer B, Martin P. The cellular and molecular basis of inflammation in fish. *International Journal of Developmental Biology*. 2006;50(2-3):241–250.
43. Roulston A, Marcellus RC, Branton PE. Viruses and apoptosis. *Annual Review of Microbiology*. 1999;53:577–628.
44. Rapi E, Droin N, Solary E. Manipulation of antigen presentation by intracellular bacteria. *Trends in Immunology*. 2017;38(4):265–277.
45. Wyllie AH. Cell death: A new classification separating apoptosis from necrosis. *Nature Reviews Molecular Cell Biology*. 2010;11(3):235–242.
46. Ramakrishnan L. Revisiting the role of the granuloma in tuberculosis. *Nature Reviews Immunology*. 2012;12(5):352–366.

47. Cortés M, Oliver C, Sánchez P, Sánchez F, Maisey K, Valdés N, Imarai M. Structure and expression kinetics of *Piscirickettsia salmonis* *sdhA* during infection of Atlantic salmon macrophage-like cells. *Fish & Shellfish Immunology*. 2025;110929.
48. Gómez FA, Milesi B, Marshall SH. Free-living amoebae and their role in *Piscirickettsia salmonis* transmission in Chilean Salmon aquaculture: insights from in vitro and in vivo studies. *Frontiers in Microbiology*. 2025;16:1711258.
49. Kumar P, Cameron J, Saviola B, Venketaraman V. *Mycobacterium marinum* immune evasion in zebrafish. *Pathogens*. 2025;14(9):908.
50. Swaim LE, Connolly LE, Volkman HE, Humbert O, Born DE, Ramakrishnan L. *Mycobacterium marinum* infection of adult zebrafish causes caseating granulomatous tuberculosis and is moderated by adaptive immunity. *Infection and immunity*. 2006;74(11):6108-6117.
51. Hansen JD, Ray K, Chen PJ, Yun S, Elliott DG, Conway CM, Soto E. Disruption of the *Francisella noatunensis* subsp. *orientalis* *pdpA* Gene Results in Virulence Attenuation and Protection in Zebrafish. *Infection and Immunity*. 2021;89(11).
52. Aguilar M, Isla A, Barrientos CA, Flores-Martin SN, Blanco JA, Enríquez R, Yañez AJ. Genomic and proteomic aspects of p57 protein from *Renibacterium salmoninarum*: characteristics in virulence patterns. *Microbial Pathogenesis*. 2023;174:105932.
53. Zhang L, Ni C, Xu W, Dai T, Yang D, Wang Q, Liu Q. Intramacrophage infection reinforces the virulence of *Edwardsiella tarda*. *Journal of bacteriology*. 2016;198(10):1534-1542.
54. Saldarriaga-Córdoba M, Avendaño-Herrera R. Comparative pan-genomic analysis of 51 *Renibacterium salmoninarum* indicates heterogeneity in the principal virulence factor, the 57 k D a protein. *Journal of Fish Diseases*. 2022;45(8):1173-1188.
55. Aguilar M, Isla A, Barrientos CA, Flores-Martin SN, Blanco JA, Enríquez R, Yañez AJ. Genomic and proteomic aspects of p57 protein from *Renibacterium salmoninarum*: characteristics in virulence patterns. *Microbial Pathogenesis*. 2023;174:105932.
56. Vasquez I, Soto-Davila M, Hossain A, Gnanagobal H, Hall JR, Santander J. Dual-seq transcriptomics of *Aeromonas salmonicida* infection in Atlantic salmon (*Salmo salar*) primary macrophages reveals lysosome and apoptosis impairments. *Fish & shellfish immunology*. 2025;162:110359.
57. Juárez-Cortés MZ, Vázquez LEC, Díaz SFM, Cardona Félix CS. *Streptococcus iniae* in aquaculture: a review of pathogenesis, virulence, and antibiotic resistance. *International journal of veterinary science and medicine*. 2024;12(1):25-38.
58. Mahmoud-Elkamouny B, Kebbi-Beghdadi C, Greub G. Aquatic Chlamydiae: A Review of Their Roles in Fish Health. *Microorganisms*. 2025;13(9):2166.
59. Li Y, Yu X, Li P, Li X, Wang L. Characterization of the ferric uptake regulator *Va Fur* regulon and its role in *Vibrio anguillarum* pathogenesis. *Applied and Environmental Microbiology*. 2024;90(11):e01508-24.
60. Larsen MH, Boesen HT. Role of flagellum and chemotactic motility of *Vibrio anguillarum* for phagocytosis by and intracellular survival in fish macrophages. *FEMS microbiology letters*. 2001;203(2):149-152.

How to cite this article: Funde A, Bhalavey P, Sneha M, Kaur K, Thombre D, Kamaljeet, et al. Intracellular evasion strategies of fish pathogenic bacteria: a comprehensive review of immune subversion mechanisms. *International Journal of Advanced Biochemistry Research*. 2026;10(10):292-298. doi: <https://www.doi.org/10.33545/26174693.2026.v10.i10d.10381>

Authors

Aniket Funde

College of Fisheries Science, CCS Haryana Agricultural University, Hisar India.

Pallavi Bhalavey

College of Fisheries Science, CCS Haryana Agricultural University, Hisar India.

Manupati Sneha

ICAR - Central Institute of Fisheries Education, Versova, Mumbai, Maharashtra, India

Komalpreet Kaur

Guru Angad Dev Veterinary and Animal Sciences University, Ludhiana, Punjab, India

Dipalee Thombre

National Facility for Biopharmaceuticals, G.N.Khalsa College, Mumbai, Maharashtra, India

Kamaljeet

Guru Angad Dev Veterinary and Animal Sciences University, Ludhiana, Punjab, India

Shruthi HU

College of Fisheries Science, CCS Haryana Agricultural University, Hisar India.

Isha Kumari

College of Fisheries Science, CCS Haryana Agricultural University, Hisar India.