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Effects of host cholesterol availability and distribution over the susceptibility of infection with *Piscirickettsia salmonis*

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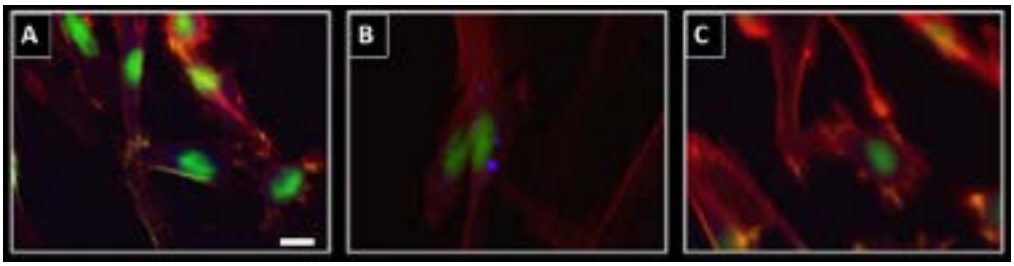
Statement of the Problem: Chile is one of the principal salmon producers in the world, even though this industry has confronted severe economic losses due to infectious diseases in recent years (1). The most important infectious disease in the history of the Chilean salmon farming is the Salmonid Rickettsial Septicaemia (SRS), which is produced by Piscirickettsia salmonis, a gram negative facultative intracellular bacterium, phylogenetically related to *Legionella pneumophila* and *Coxiella burnetii* pathogens (2). These bacteria share the capacity to replicate within host membrane-bound cytoplasmic bacteria-containing vacuoles (BCVs) to facilitate their intracellular replication and survival. The formation and maintenance of the BCVs are dependent on the capacity of the bacteria to manipulate host cell vesicular trafficking pathways, which in turn, is dependent of the host cholesterol metabolism (3). The purpose of this work is to study if changes in the abundance and distribution of cholesterol in salmon cells affect the entry and/or intracellular proliferation of Piscirickettsia salmonis. Methodology & Theoretical Orientation: The alteration of biosynthesis of endogenous cholesterol in salmon cell lines was induced by using HMG-CoA reductase inhibitors (*statins drugs*) (4), while intracellular cholesterol distribution was induced by the NPC1 protein inhibitor (U18666A drug) (5), which produces cholesterol accumulation in late endosomal/lysosomal compartments (Niemann-Pick C disease phenotype). The infection capacity of *Piscirickettsia salmonis* was evaluated in vitro following the typical cytopathic effect (CPE) of cells during infection progression by IFAT, while the intracellular bacterial load was quantified by qPCR. Findings: The results indicated that salmon cell lines exposed to increased doses of statins and U18666A (non cytotoxic neither antibiotic concentrations) showed a decreased susceptibility to infection with Piscirickettsia salmonis, phenotype that can be partially reversed by mevalonate and MβCD, respectively. Conclusion & Significance: The results indicated that disturbing cholesterol drugs and the modulation of the cholesterol availability in fish could be possible strategies to combat SRS.



Recent Publications

1. Rozas M, Enriquez R. (2014). Piscirickettsiosis and *Piscirickettsia salmonis* in fish: a review. Journal of fish diseases 37, 163 -188.
2. Gómez FA, Tobar JA, Henriquez V, Sola M, Altamirano C, Marshall SH. (2013). Evidence of the presence of a functional Dot/Icm type IV-B secretion system in the fish bacterial pathogen Piscirickettsia salmonis. PLoS One 8, e54934.
3. Isberg RR, O'Connor T, Heidtman M. (2009). The Legionella pneumophila replication vacuole: making a cozy niche inside host cells. Nature Reviews. Microbiology, 7(1), 13–24.

4. Bedi O, Dhawan V, Sharma PL, Kumar P (2016). Pleiotropic effects of statins: new therapeutic targets in drug design. Naunyn Schmiedebergs Arch Pharmacol.

5. Schultz ML, Krus KL, Lieberman AP. 2016. Lysosome and endoplasmic reticulum quality control pathways in Niemann-Pick type C disease. Brain Res. 26. pii: S0006-8993(16)30166-4.

Biography

Rodrigo Pulgar has his expertise in studying host-pathogen interactions, focusing his research in salmonid intracellular bacterial infections. Since 2016, he has been studying the susceptibility effects of salmon macrophages to *Piscirickettsia salmonis* and Renibacterium salmoninarum infection, specially associated to the effects of nutritional requirements and host cholesterol availability and distribution to accomplish bacterial infection. These two bacteria generate infections that cause major economic losses in the salmonid Chilean industry, and which currently have no effective prophylactic treatments. His striking recent results in cell culture have led to a promissory opportunity to apply his findings in whole fish by using new funds he have reached during 2017 and 2018.

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