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From Trash to Treasure: The Story of Fish Proteasomes

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Abstract

Proteasomes, once regarded as cellular waste-disposal units, are now recognised as regulators of fish immune function, stress adaptation and protein homeostasis. This article explores the structure and function of the proteasome, the targeted protein degradation by the ubiquitin-proteasome system (UPS) and its regulation in response to environmental stressors. These molecular machines control antigen presentation, starvation, hypoxia, oxidative and heat stress and oocyte maturation in fish. They act as stress biomarkers and disease resistance enhancers in aquaculture. Targeted proteasomal degradation of proteins is made possible with recent technologies like PROTACs (Proteolysis Targeting Chimaeras) that could help in precision aquaculture.

Keywords: Aquaculture, Fish biology, Proteasomes, Stress adaptation

Introduction

Fish can survive in the harshest parts of our planet's waters, from the frigid Antarctic to oxygen-depleted wetlands. Their secret, invisible weapon responsible for their adaptation, is a small protein degrader that works constantly. They are proteasomes that grind up damaged, misfolded or no longer needed proteins. But they are more than just janitors. They are stress responders, fish immunity guardians, muscle managers and brain protectors. Regardless of climate change, proteasomes emerge as surprising leads in fisheries science, allowing fish to thrive and has become the matter of study for scientists who reconsider how we sustain aquatic life in a changing environment.

What Are Proteasomes?

Proteasomes are the high-tech cylindrical protein shredders composed of a 26S multi-subunit barrel-shaped complex conserved across all eukaryotes. The 20S core, a four-ringed structure (α-β-β-α), is the heart of the proteasome. β rings act as protease sites and are specialised to cut proteins at acidic (β1), basic (β2) or hydrophobic (β5) residues, while the outer α-rings act as gated doors. 19S regulatory particle is a cap sitting on one or both ends of the 20S core and plays the roles of bouncer, recruiter and ATP-powered unwinder. It's made up of multiple subunits, including ATPases that open the α-ring gate by binding to conserved regions and drag in unfolded proteins.

Targeted Protein Degradation

Misfolded, oxidatively damaged, truncated, or excess proteins are often broken down by UPS to maintain protein homeostasis. Damage signals that alarm breakdown include exposed hydrophobic patches, chaperone refolding failure, or destabilising N-terminal residues (N-end rule). E1, E2 and E3 help in activating ubiquitin and targeting the substrate to transfer the ubiquitin onto a lysine residue on the protein. This iterative process results in polyubiquitin chain linked through lysine-48 (K48), which acts as a degradation signal. The 19S cap recognises the ubiquitinated protein through receptors (Rpn10/Rpn13) and the ubiquitin chain is broken down for recycling by deubiquitinases (DUBs: Rpn11, UCH37, USP14). Following its unfolding by AAA+ ATPases (Rpt1-Rpt6), the substrate is moved into the 20S core and cleaved into peptides by catalytic β-subunits. These peptides can be further broken down into amino acids for energy and biosynthesis. They can also be utilised in immune surveillance, particularly in antigen-presenting cells, which are carried into the ER, loaded onto MHC Class I molecules and presented on the cell surface so that cytotoxic T cells can recognise them. The holistic diagram representing the UPS mechanism is given in figure 1.

Article History

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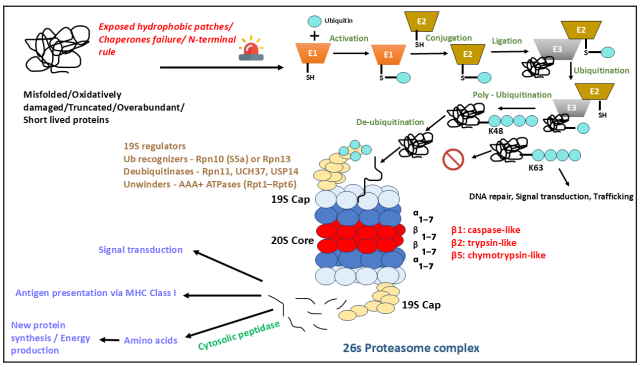

Figure 1: Mechanism of protein degradation in the Ubiquitin Proteasomal System (UPS)

Regulation of Proteasome Activity

In addition to the well-known 26S and immunoproteasomes, cells also produce a variety of other proteasomes to carry out different functions. Examples include thymoproteasomes, which help train immune cells, hybrid forms that combine multiple functions, the 20S core, which activates under stress and PA28 or PA200-capped types, which help repair DNA and fine-tune peptides. Nrf1 helps to adapt proteasome production to the quantity of protein waste the cell must handle by tightly controlling the proteasome's protein breakdown process. Biological modifications (like phosphorylation) and the attachment of multiple regulatory caps to the core of the proteasome also affect its capacity to choose and degrade proteins. Proteasomes become more functional when they come into contact with stressors such as oxidative damage, infection, or temperature shock. The reversible disassembly of the 26S at normal conditions releases the 20S core for ATP-independent destruction. Proteins like Ecm29 often aid in this process.

Why Proteasomes are a Treasure for Fisheries Research?

Understanding proteasome dynamics can help identify stress biomarkers, improve disease resistance breeding and increase survival under intensive aquaculture, where fish are subjected to temperature fluctuations, pathogens, hypoxia and stress (Figure 2).

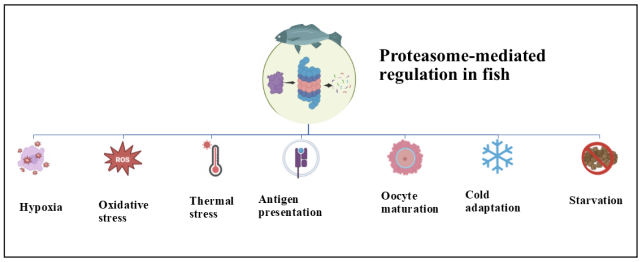

Figure 2: Proteasome-mediated regulation in fish for oocyte maturation and in response to environmental stressors

Adaptation to Hypoxia

Due to hypoxia, the protein degradation relies mainly on the core 20S proteasome rather than the 26S proteasome since the ATP levels are low. HIF-1α regulates the hypoxia response. In normoxic conditions, the UPS consistently destroys HIF-1α. During hypoxia, Slower UPS degradation of HIF-1α can activate angiogenesis and anaerobic metabolism genes. Changes in proteasome gene expression fine-tune the hypoxia-induced stress response by overexpression of particular 20S subunits and deubiquitinases (Li *et al*., 2025).

Response to Oxidative Stress, Starvation and Growth

Cells' direct quenching of reactive oxygen species is the first line of defence against oxidative stress. The UPS offers a secondary defence mechanism *via* degradation of abnormal proteins by cellular redox status. Nrf2 is a transcription factor that activates antioxidant enzymes but is continuously ubiquitinated and degraded *via* the proteasome under normal conditions. When cell senses oxidative stress, Nrf2 is moved into the nucleus, triggering the expression of antioxidant response elements associated genes. Fish tissues like liver and gill have shown upregulated 20S activity under oxidative stress (*e.g.*, exposure to cadmium), suggesting it's a frontline defence mechanism. Starvation causes significant downregulation of the UPS pathway. The fish with a better growth performance exhibits a higher UPS activity with high expressions of *ub*, *chip* and *psmc1* in parallel with the activation of protein synthesis (Nemova *et al*., 2021).

Influence of Water Temperature on Proteasome Function

Temperature is a major regulator of proteasome activity in fish and both cold-adapted species and those under thermal stress show fascinating proteasome tuning strategies to maintain protein homeostasis (Li *et al*., 2023). Cold-adapted fish upregulate 20S and 26S proteasome subunit genes, ensuring a steady supply of degradation machinery even when protein turnover is naturally sluggish. Due to thermal stress, protein misfolding often occurs, which leads to activation of chaperones - HSPs (Heat Shock Proteins). If refolding fails, the proteins are sent to UPS. In addition to this, high temperature leads to increase in expression of proteasome subunits, E2/E3 enzymes and ubiquitin genes. Understanding proteasome responses to temperature helps us identify stress-tolerant fish breeds, develop temperature biomarkers and design better climate-resilient aquaculture systems.

Role of Immunoproteasomes in Fish Immunity

Interferon-γ produced in fish immune cells in response to infection tends to replace common proteasome subunits (β1, β2, β5) with immune-specific subunits (β1i (LMP2), β2i (MECL-1) and β5i (LMP7) forming immunoproteasomes. These proteasomes generate particular peptide fragments, which are transported into the ER by TAP and loaded onto MHC class I for antigen presentation. Antiviral immune response in lung fish showed increased expression of immunoproteasomal β subunits. LMP7 was found to be upregulated in the brain of the seven-band grouper following Nervous Necrosis Virus (NNV) infection and negatively regulates cytokine responses by interfering with NF-κB signalling (Krishnan *et al*., 2021).

Proteasome Role in Oocyte Maturation

Fish oocyte maturation is a multi-step process involving gonadotropin (LH), maturation-inducing hormone (MIH) and the maturation-promoting factor (MPF), a cyclin B and cdc2 kinase complex. Cyclin B is synthesised *de novo* when

MIH is stimulated, activating cdc2 kinase, generating active MPF and pushing the oocyte from prophase arrest to meiosis metaphase. The controlled degradation of cyclin B at lysine 57 in the NH_2 terminus by proteasome inactivates MPF, which is required for meiosis completion and fertilisation (Kodzik *et al*., 2024).

Conclusion

These cellular cleaners are now stepping into the spotlight as regulators of fish health, stress resistance and immunological defence. This shift in understanding in their roles has made them crucial assets for future aquaculture and fisheries. Proteasomal activity and gene expression are emerging as early indicators of stress and disease for monitoring fish health. They can be applied in the selective breeding for producing climate-resilient fish. PROTACs (Proteolysis Targeting Chimeras) are paving the way for targeted protein interventions in fisheries as in human therapeutics. By selectively degrading proteins linked to stress, disease, or poor adaptability, PROTACs offer a powerful tool to boost fish welfare and marking the rise of precision aquaculture powered by proteasome biology.

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