Researchers reveal similarities between fish and humans

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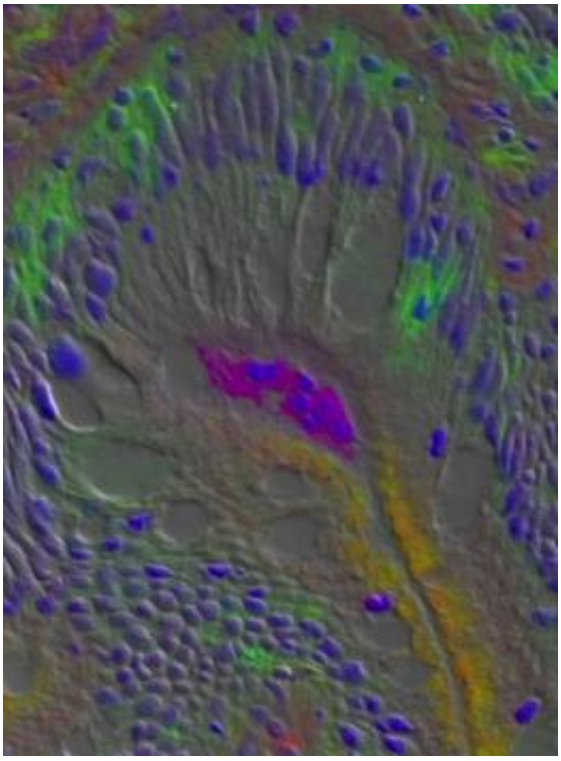

This is a gut section from an infected fish showing the presence of IgT+ B cells (green) in the epithelium and the parasite *C. shasta* (magenta). Credit: University of Pennsylvania

A study at the University of Pennsylvania School of Veterinary Medicine has identified the function of one of the earliest antibodies in the animal kingdom, an ancient immunoglobulin that helps explain the evolution of human intestinal immune responses. It was discovered to

play a predominant role in the guts of fish and paves the way for a better understanding of human gut immunity as well as for safer, healthier approaches to keeping fish from pathogen infections. The findings appear in the online version of *Nature Immunology* and will be featured on the cover of the September issue.

The study identified unique aspects of the structure and function of a fish antibody, IgT, and points to this molecule as the most ancient vertebrate immunoglobulin specialized in mucosal immunity. The findings challenge the present paradigm that specialization of immunoglobulin isotypes into different body areas, i.e., intestine and blood, arose during the evolution of four-legged creatures, or tetrapods. While IgT was discovered five years ago, its structure and function remained an enigma.

In addition to characterizing the protein structure of IgT, the study provides direct evidence for the existence of a novel B cell lineage uniquely producing IgT. In the gut, IgT+ B cells represent the predominant B cell subset. More critically, the study showed that responses of rainbow trout IgT to an intestinal parasite were only detected in the gut, whereas IgM responses were confined to plasma. Supporting further the role of IgT in mucosal immunity, the researchers found that a majority of trout intestinal bacteria were coated with IgT. The research team concluded that the specialization of immunoglobulin isotypes into different body compartments is a universal feature of all jawed vertebrate immune systems, a feature required for health maintenance in environmentally different exposed body areas that require different immune needs.

"Immunoglobulins like IgA, IgX and the newly discovered IgT are evolutionarily distant," said Oriol Sunyer, associate professor in the Department of Pathobiology at Penn Vet. "Their specialization into mucosal compartments must have occurred independently by a process

of convergent evolution driven by similar selective pressures operating on the gut environment of fish, amphibians and mammals."

Significantly, the study shows that fish IgT and human IgA systems appear to utilize similar solutions to maintain healthy intestines, therefore Sunyer indicated that "future studies on IgT will further unravel structural and functional aspects of human mucosal immunoglobulins that are key to their role in keeping our intestines free of pathogens."

With aquaculture being the fastest growing animal food sector in the United States, as well as in the global marketplace, the findings should also impact fish health and vaccinology. In that regard, all prior studies carried out in teleost fish during the last few decades have missed the specific contribution of IgT in protecting fish from pathogens. Sunyer's studies establish that teleost fish contain not one, as originally believed, but at least two functional immunoglobulins, IgM and IgT, that respond to pathogenic challenge in different body areas. Thus, the new capability of measuring not only IgM but also IgT responses will greatly facilitate the evaluation and understanding of fish immune responses as well as the protective effects of fish vaccines.

"The design of future fish vaccines is likely to be more effective, stimulating not only systemic but also mucosal immunity as we are now able to measure IgT-induced responses," Sunyer said.

"Dr. Sunyer's work will change how we look at disease prevention in fish, and his breakthrough will have a profound impact on the future of the aquaculture industry," said Roger Beachy, director of the National Institute of Food and Agriculture. "I am proud that the USDA supports such innovative research."

Immunoglobulins first emerged in vertebrates around 400 million years

ago along with the appearance of the jawed fish, the most ancient living vertebrate species with jaws. Throughout evolutionary time, immunoglobulins diversified into several isotypes with specialized roles in innate and adaptive immunity in different parts of the body, according to the study's author, who says the study of immunoglobulins from fish and other animal species will continue providing new insights that are fundamental for understanding the role of these molecules in protecting us against pathogens.

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