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**Overview**

# Getting the Inside Tract: New Frontiers in Zebrafish Digestive System Biology

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The establishment of the zebrafish as a prominent model organism was largely driven by the desire of developmental biologists for a genetically tractable system for understanding early vertebrate embryogenesis.[1] The pioneering studies using zebrafish embryos were largely focused on genetic analyses of early development and organogenesis during the first 3 days postfertilization (dpf). During these early studies, a number of mutants displaying defects in one of the key digestive organs—the intestine, liver, and pancreas—were identified and have since been intensively studied. Prior to these efforts, other researchers utilized zebrafish larvae for toxicity studies as many of the same reasons that make this system attractive to geneticists also make them an excellent model for toxicology,[2,3] including their prolific breeding in captivity, transparency of the embryos, and their simple culture systems. The collective success of these studies led to an expansion of the community of zebrafish researchers and the establishment of zebrafish as a cornerstone model used by the broader biomedical research community.

Zebrafish research in digestive organs began with early large-scale genetic screens, one of which included a gastroenterologist (Michael Pack).[4] The combined accomplishments of this and the efforts of other researchers carrying out genetic and chemical screens[5–7] clearly demonstrate the utility of the zebrafish system to investigate digestive system development and physiology. Patterning and development of the individual digestive organs from the endoderm largely begins after the first day of development only after the major embryonic axes are established. Digestive tract function ramps up after 5 dpf when yolk has been completely utilized. This stage of development has been viewed by classical zebrafish researchers as very late, when much of larval patterning and pigmentation is already complete, limiting some of the advantages of imaging embryos at earlier stages. Regardless, at these later larval stages, many of the functions of the digestive organs are analogous to their counterparts in mammals. Thus, the early larvae can be used to study many processes that are associated with mature organs that in other organisms can only be studied in adults. Now many investigators take advantage of the same attributes that make zebrafish a powerful system for studying embryogenesis to understand postembryonic processes and model human diseases. Indeed, as the scope of zebrafish research has expanded in size and sophistication, exciting new areas of postembryonic biology have been explored, including the maturation, function, and pathology of digestive organs.[5,8–12] As illustrated in the articles included in this special issue of *Zebrafish*, research on the development of the zebrafish digestive system includes many new exciting areas, such as enervation of the intestine and development of the biliary tract and the endocrine and exocrine pancreas.

Diseases affecting the digestive system in humans range from rare genetic disorders that impair gut motility and developmental defects such as Alagille's syndrome that cause atresia of the biliary tract to diseases attributed in part to environmental exposures such as type II diabetes, alcoholic liver disease, and inflammatory bowel disease. Remarkably, the pathology of zebrafish with similar disorders often mirrors human diseases, making this an outstanding system to study hepatobiliary, gastrointestinal, and pancreatic diseases. For instance, many of the features of fatty liver disease, which in humans is typically caused by metabolic syndrome or alcohol abuse, are similar in zebrafish, as described in this issue by Howarth *et al.*[13]

The zebrafish has also been a useful model for investigating the mechanisms underlying intestinal injury and inflammation. Oehlers and colleagues describe in this issue, diverse methods for inducing and evaluating intestinal injury, providing new models of human inflammatory bowel disease.[14] Another exciting translational area of zebrafish digestive system research is in the relationship between the complex community of microorganisms residing in the intestine (gut microbiota) and host physiology. A study by Toh and colleagues (this issue) tests the ability of anaerobic bacteria de-

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rived from the human intestine to colonize the zebrafish gut, suggesting that the zebrafish could be used as an experimentally malleable system for modeling host–microbiota interactions in humans.[15]

While most researchers are drawn to the ease of working with zebrafish embryos and larvae, a number of important studies have focused on processes that occur in adults. For instance, several groups have made significant advances in studying genetic models of a range of cancers (as reviewed in[16–18]). In this issue, Paquette *et al.* describe a survey of spontaneous gastrointestinal neoplasia across a range of adult wild-type fish,[19] which will serve as a benchmark for assessing changes in tumor incidence in genetically modified fish in the future. Moss and colleagues (this issue) overcome one of the major barriers of using imaging to study adult physiology by using transparent *Casper* adults[20] to visualize regenerative growth of cells in the pancreatic islets in adult zebrafish.[21]

Although *ex vivo* studies have laid much of the groundwork for our biochemical understanding of digestive organ physiology, they do not replicate the complex interplay of neural, chemical, hormonal, and environmental cues that regulate digestive organ physiology *in vivo*. Historically, live cells are often cultured on artificial surfaces, yet this lacks input from adjacent cells and tissues—that is, the cell microenvironment. These limitations are overcome by using zebrafish as a whole animal system, where digestive organs such as the intestine contain microorganisms, bile, and mucus that each influence physiology and, importantly, the development of pathology.[4,9,22–26] For these reasons, *in vivo* studies are vital for answering many long-standing questions of digestive organ physiology. While the small size of zebrafish pose some limitations, such as collecting serum for metabolic and physiological studies, a number of innovative approaches are being developed to circumvent these limitations. Thus, as highlighted by the exciting research in this issue, the tractability of zebrafish makes it the ideal system to tackle questions of digestive organ function at the cellular level. Despite the immense potential of the zebrafish as a therapeutic screening tool and system for physiological studies at the subcellular level, it is currently underutilized by both the academic and pharmaceutical research communities. The work described in this special issue will hopefully contribute to changing this state of affairs.

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