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Antigen sampling in the fish intestine

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ABSTRACT

Antigen uptake in the gastrointestinal tract may induce tolerance, lead to an immune response and also to infection. In mammals, most pathogens gain access to the host through the gastrointestinal tract, and in fish as well, this route seems to be of significant importance. The epithelial surface faces a considerable challenge, functioning both as a barrier towards the external milieu but simultaneously being the site of absorption of nutrients and fluids. The mechanisms allowing antigen uptake over the epithelial barrier play a central role for maintaining the intestinal homeostasis and regulate appropriate immune responses. Such uptake has been widely studied in mammals, but also in fish, a number of experiments have been reported, seeking to reveal cells and mechanisms involved in antigen sampling. In this paper, we review these studies in addition to addressing our current knowledge of the intestinal barrier in fish and its anatomical construction.

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1. Introduction

Compared with mammals, studies of the mucosal barrier and antigen uptake in the gastrointestinal (GI) tract of fish are in their infancy. Particulate antigen sampling in the mammalian intestine is generally considered to occur mainly via M cells in addition to dendritic cells and macrophages which may extend protrusions through the epithelial barrier into the intestinal lumen. A limited number of studies have addressed such features of the fish GI tract, but the mechanisms of antigen uptake are not yet fully understood. As numerous infectious organisms gain access to the host through the intestines and because novel vaccine approaches in the finfish industry should concentrate on oral delivery approaches, the information on the epithelial barrier, its selectiveness and response to antigen are pivotal for success. In modern bony fishes or teleost fish, the hind region of the intestine has often been described as the most important intestinal region for macromolecular uptake and immune induction. However, the full picture of the nature of the cells and mechanisms involved in the antigen sampling are still to be unraveled. In addition, the differing and confusing anatomical nomenclature used by many researchers and a substantial variation in the construction of the GI tract between different fish species makes it difficult to sort out the information available. In this review, we aim at clarifying anatomical features of the teleost

intestine and put this information in context with the information available regarding antigen uptake. We will focus on the mechanisms of antigen sampling across the epithelial barrier, and only briefly address induction of immune responses following intestinal antigen exposure recently reviewed by others (Rombout et al., 2014; Salinas et al., 2011). As most knowledge with respect to intestinal antigen sampling is related to mammals, we cannot avoid referring to mammals in this review, but the focus will be on the situation in teleost fish where such information is currently available.

Mucosal surfaces, in fish including those of the GI tract, skin, gills and the olfactory organ, are in close encounter with multitudes of antigens and most infectious agents enter the host through mucosal membranes. Antigens may be used as a common term for structures capable of binding to an antibody or T cell receptor and hence have the ability to initiate an adaptive immune response (Parham, 2009b). In overview, the intestinal *mucosa* exerts a double function, being responsible for nutrient and fluid absorption but at the same time creating a tight and selective barrier towards the external environment. The intestine moreover homes thousands of commensal bacteria, which play important roles in digestion and immunity and even affect the intestinal morphology (Goto and Ivanov, 2013; Merrifield et al., 2009). For the intestinal *mucosa*, immune tolerance or unresponsiveness is hence immensely important, securing that defense responses should only occur towards pathogens and not towards material such as food proteins or harmless microbes (Sansonetti, 2004). In teleost fish, oral tolerance

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is recognized to be a significant mechanism, however the details behind the phenomenon are still not known (Rombout et al., 2014).

In mammals, surveillance of the intestinal luminal content is carried out by specialized M cells in the intestinal epithelium which sample antigens and transport them to underlying macrophages or dendritic cells (Jang et al., 2004). These professional antigen-presenting cells again activate immune cells within the underlying lymphoid follicles. In the steady state of mammals, induction of intestinal immune responses is mainly dominated by local production of immunoglobulin A (IgA) secreted into the intestinal lumen to prevent pathogens from entering tissue compartments (Menard et al., 2010). In teleost fish, most reports on intestinal antigen uptake have ascribed the uptake to the regular absorptive enterocytes (Rombout et al., 2011). However, in the Atlantic salmon (*Salmo salar* L.), epithelial cells absorbing gold-BSA with diverging features from the adjacent enterocytes were suggested to have some similarities with immature mammalian M cells (Fuglem et al., 2010). Teleost fish do however not possess lymphoid aggregates in the mucosal membranes, but the intestine rather contains a diffusely organized gut-associated lymphoid tissue (GALT) comprising different immune competent cells. Additionally, mammalian IgA cannot be resolved but rather IgT has been characterized, presumed to be the immunoglobulin with prevalent function in mucosal tissues in teleost fish (Zhang et al., 2010). In mammals, the immune responses at different mucosal sites are closely orchestrated, and locally activated mucosal immune reactions are distinct from those initiated by the systemic part of the immune system (Holmgren and Czerkinsky, 2005; Mestecky et al., 1994). Also in fish, the mucosal responses of the GI tract, gills and skin appear to be integrated (Cain and Swan, 2011).

2. Gastrointestinal anatomy and the intestinal barrier

2.1. Regions of the gastrointestinal tract

Although morphologic development of the GI tract has proven to be more or less similar in all vertebrate species investigated (De Santa Barbara et al., 2003), the final structure or form of the system may differ greatly. Between mammals, there are large variations in the macroscopical construction of the GI tract. In teleost fish, GI anatomy have been closely linked with feeding habits, although the GI structure can be highly variable also in fish with similar diets (Buddington et al., 1997). Typical diversity is seen in oral cavity construction, length and topography of the GI tract, number of appendixes or pyloric caeca and in the presence of a stomach (Abbate et al., 2012; Buddington and Kuz'mina, 2000; Kapoor, 1975).

Along the GI tract, the wall has a complex topography or folding pattern. The folding is closely linked with the function of the GI regions and dictates the plasticity of the wall and the epithelial surface area. In mammals, the different regions of the GI tract are macroscopically distinct. In teleost fish however, the borders or transitions between the different functional regions are not as prominent as in mammals. Both in mammals and in fish, the intestine is usually defined as the GI tract posterior to the stomach and this definition is applied in the current review paper.

In mammals, nutrient uptake mainly occurs in the small intestine (Silverthorn, 2001). Here, circular folds or plicae, mucosal villi and enterocyte microvilli contribute to enlarge the absorptive area. Moreover, short crypts of Lieberkühn are present at the base of the villi, containing epithelial stem cells and Paneth cells that create a fairly sterile environment within the crypt pockets (Sansone, 2004). The small intestine can again be divided into the duodenum, jejunum and ileum. Aggregates of lymphoid follicles called Peyer's patches are found with high density in the ileal portion and

antigen sampling M cells in the follicle-associated epithelium are found in high numbers in this region.

In the mammalian large intestine, there are no intestinal villi but long, straight crypts or glands for water absorption and mucus secretion (Young et al., 2006). The large intestine is permanently exposed to a high load of commensal bacteria and isolated lymphoid follicles with overlying M cells are found in this region (Sansone, 2004). In teleost fish, a small and large intestine is not clearly defined and teleosts so far investigated do not have mucosal villi in the intestine but rather intestinal folds. The topography of the luminal surface varies between different species, for instance, intestinal crypts are found in the family Gadidae and in wolffish (*Anarhichas lupus* L.) but have not been identified in salmonids (Harder, 1975; Hellberg and Bjerkås, 2000; Løkka et al., 2013).

In stomachless teleosts such as cyprinids, a nomenclature has been applied dividing the intestine into a first, second and third segment as reviewed elsewhere (Rombout et al., 2011), while others have used the terms first and second segment of the mid-intestine and posterior segment, respectively (Wallace et al., 2005). The first segment begins immediately after the pyloric sphincter and consists of nutrient absorptive cells, while the following second segment is suggested as an equivalent to the mammalian ileum with cells responsible for antigen uptake (Rombout et al., 2011; Wallace et al., 2005). Finally, the third segment ending with the anus is considered as homologues to the large intestine and believed to possess osmoregulatory functions (Rombout et al., 2011; Wallace et al., 2005). Also in the Atlantic salmon, the intestine can be categorized into a mid and posterior region, where the mid-intestine again may be divided into a first and a second segment. The second segment of the mid-intestine has prominent circular folds and is considered as the region mainly responsible for antigen uptake (Fuglem et al., 2010; Løkka et al., 2013; Løkka et al., 2014b). The posterior segment has clearly different topography from the second segment of the mid-intestine with smaller irregular folds (Løkka et al., 2013), but elevated transcript levels of immune-related genes (Løkka et al., 2014a), which point to important immune-regulatory functions also of this region.

2.2. Composition of the gastrointestinal wall

The GI wall of mammals can in general be differentiated into four distinct layers, namely the *mucosa*, the *submucosa*, the *muscularis* and finally the *serosa* (Young et al., 2006). In teleost fish, this overall organization can be recognized, but with some variations. The *mucosa* forms the lining towards the intestinal lumen. In mammals, it consists of a single layered columnar epithelium covered by mucus, the underlying connective tissue called the *lamina propria* and a thin layer of smooth musculature called *muscularis mucosa*. In teleost fish, the *muscularis mucosa* is often missing. Rather, a distinct thick layer of elastic fibers, called the *stratum compactum*, is present in several teleost species and usually considered as part of the *mucosa*. High densities of eosinophilic granular cells, creating a band named the *stratum granulolum*, are also typically present in the *mucosa* of teleost fish and are suggested as analogues to mammalian mast cells (Hellberg et al., 2013). The next structure, the *submucosa*, is a deeper layer consisting of loose connective tissue. The *submucosa* is often not defined as a separate layer in teleosts. Further, the *muscularis* consists of muscle fibers creating two sheets due to the different fiber directions. The direction of the stratified muscle fibers can however typically switch along the GI tract, being opposite in the esophagus and first part of the stomach compared to the intestine which has an inner circular and an outer longitudinal muscle layer. Finally, the *serosa*, a thin coating of connective tissue and a squamous epithelium, defines the outer lining of the GI wall.

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