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Mast cells in gastrointestinal disorders

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ABSTRACT

Mast cells are constitutively found in the gastrointestinal (GI) tract. The three major physiological functions of GI mast cells comprise of – as far as we know – regulation of GI functions, namely epithelial and endothelial functions, crosstalk with the enteric nervous system, and contribution to the host defense against bacterial, viral and parasitic agents. A number of chronic GI diseases, including inflammatory bowel disease (Crohn's disease, ulcerative colitis), celiac disease, irritable bowel syndrome, and food allergies, are thought to be associated with mast cell hyperplasia and humoral activity. Clinical conditions characterized by a decrease in mast cell functionality are not known so far. In the present review, we summarize current evidence which show that human mast cells play a central role at the GI barrier, both in health and disease.

1. Localization of mast cells in the healthy GI tract

Mast cells are preferentially located at interfaces where the host and environment meet such as the mucosa of the GI tract. Indeed, mast cells are found in the healthy human intestinal mucosa, preferentially in the lamina propria, where 2 – 3% of the cells are mast cells (Fig. 1). The intestinal mucosa is the largest interface of the human body (estimated 200–400 m^2), and a most challenging one because the intestine hosts a large number of bacteria that need to be controlled to prevent invasion of the host. To do this, the intestine is equipped with a unique barrier, comprising not only of the mucosa, but also mucosal secretagogues, like mucus and anti-bacterial peptides, muscle layers, which enable peristalsis, and the enteric nervous system, which mediates defense programs that result in enhanced secretion and motility, and finally diarrhea (Bischoff et al., 2014). Many of these barrier functions are regulated by GI mast cells. Numerous intestinal and extraintestinal disorders are thought to be associated with an impaired GI barrier function as well as with mast cell actions (Table 1).

Human mast cell subtypes have been defined based on their protease content. In the intestinal mucosa, most mast cells belong to the tryptase positive, chymase negative subtype (MC_T), resembling the mucosal mast cell subtype in rodents. In the submucosa, mast cell density is lower (about 1% of all cells) compared to the mucosal lamina propria, and the majority of submucosal mast cells are tryptase, a chymase double positive mast cell subtype (MC_{TC}), corresponding to the connective tissue mast cells subtype in rodents (Bischoff, 2009; Galli and Tsai, 2010). In the course of disease, the number of mast cells can change dramatically. For example, mast cell density may increase more than 10 fold, from 2 – 3% up to 30 – 50% of lamina propria cells in patients with GI manifestations of mastocytosis (Bischoff, 2009), as shown in Fig. 1.

2. Physiological function of GI mast cells

2.1. Effector functions of GI mast cells

Human mast cells have been established as the key effector cells of allergic inflammation. Indeed, they act as cellular mediators of allergic inflammation, including in the intestine (Bischoff, 2007; Bischoff and Sampson, 2012); however, they not only regulate allergies, but also many physiological tissue functions (Fig. 2). In the intestine, mast cells regulate blood flow, smooth-muscle contraction and peristalsis, mucosal secretion, and innate and adaptive immune responses (Bischoff, 2009; Frossi et al., 2010; Galli and Tsai, 2010). This explains why mast cells are involved in so many different types of GI diseases not only allergic disorders, but also GI infections and chronic inflammatory disorders, colon cancer and other malignancies (Table 1).

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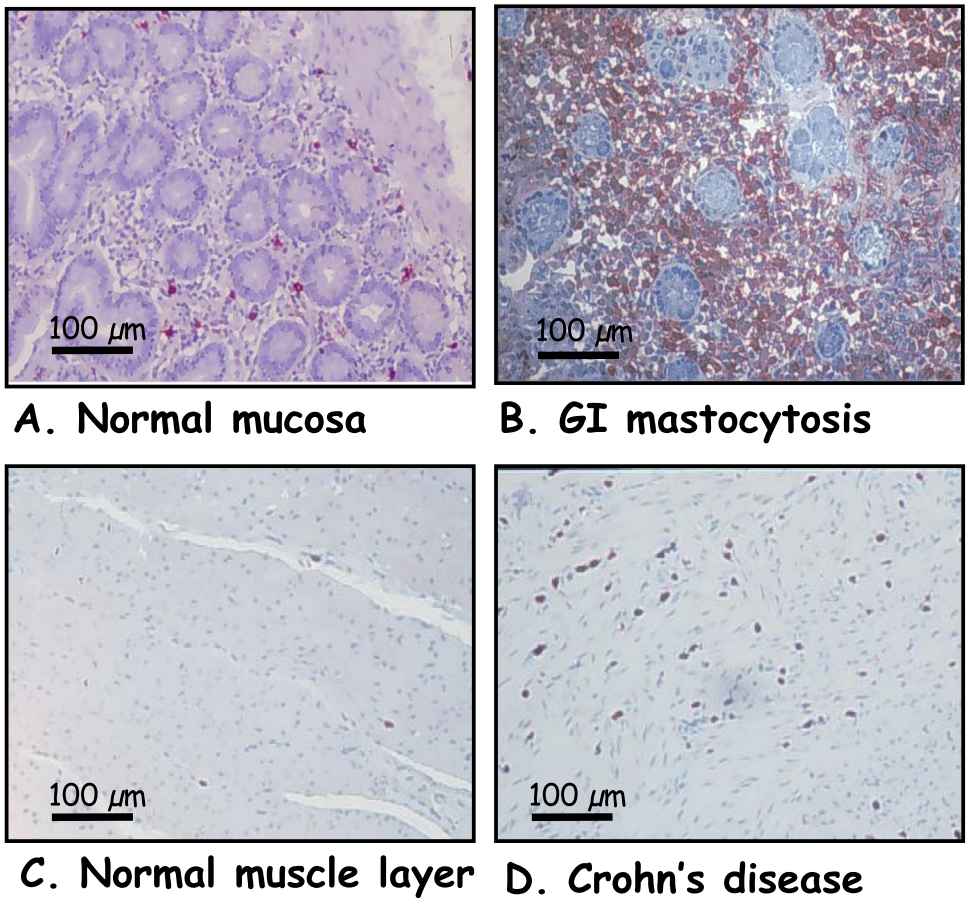

Fig. 1. Mast cell hyperplasia in GI diseases. A, B) Mucosal mast cell hyperplasia in a patient with GI mastocytosis. C, D) Smooth muscle mast cell hyperplasia in a patient with fibrotic Crohn's disease.

Table 1
Inflammatory GI diseases that have been associated with mast cells.

Type of disease	*Examples*	*References*
Adverse reactions to food[a]	Food allergy manifesting in the GI tract	(Bischoff and Crowe, 2005; Bischoff, 2007; Bischoff et al., 1997; Bischoff and Sampson, 2012; Pickert et al., 2012)
	Celiac disease	(Lahteenoja et al., 2000; Lavö et al., 1989; Marsh and Miller, 1985; Strobel et al., 1983)
Inflammatory bowel disease[a] (IBD)	Crohn's disease	(Bischoff et al., 1996; Brenner et al., 2014; Farhadi et al., 2007; Gelbmann et al., 1999; Kobayashi et al., 2007; Okumura et al., 2009; Raithel et al., 2001)
	Ulcerative colitis	(Bischoff et al., 1996; Farhadi et al., 2007; Raithel et al., 2001; Stoyanova and Gulubova, 2002)
Irritable bowel syndrome[a] (IBS)	Diarrhea-type IBS	(Buhner et al., 2009; Klooker et al., 2010; Stefanini et al., 1995; Vivinus-Nébot et al., 2011; Weston et al., 1993)
	Pain-type IBS	(Barbara et al., 2004; Barbara et al., 2007; Buhner et al., 2009; Klooker et al., 2010; Weston et al., 1993)
Infectious GI diseases[a]	Bacterial gastroenteritis	(Abraham and St. John, 2010; Bischoff and Krämer, 2007; Raqib et al., 2003; Scheb-Wetzel et al., 2014)
	Helicobacter infection	(Caruso et al., 2011)
	Parasitic infection	(Abraham and St. John, 2010; Ball and Hay, 1990; da Silveira et al., 2007; Finkelman et al., 2004; Hepworth et al., 2012)
	Viral enterocolitis?	(Becker et al., 2014; Kulka and Metcalfe, 2006; Lappalainen et al., 2013)
Malignant GI diseases	Intestinal polyps[b]	(Cheon et al., 2011; Gounaris et al., 2007; Maywald et al., 2015)
	Colon cancer[c]	(Ammendola et al., 2014; Blatner et al., 2010; Wu et al., 2012)
	GI mastocytosis[c]	(Akin and Valent, 2014; Behdad and Owens, 2013; Pardanani, 2015; Siebenhaar et al., 2014)
Other	Microscopic colitis[c]	(Baum et al., 1989; Yen and Pardi, 2011)

[a] For details see text.
[b] Only mouse data, not discussed in the present review.
[c] Not discussed in the present review.

GI mast cells, as with mast cells found in other locations, exert their biological functions preferentially by humoral functions. They can release a range of mediators, mostly upon stimulation, which further explains how mast cells can be involved in so many physiological and pathophysiological processes. The human GI mast cell mediators comprise of amines (histamine, serotonin), cytokines, proteases, lipid mediators (leukotrienes, prostaglandins), and proteoglycans such as heparin (Bischoff et al., 1999a; Gebhardt, 2005; Lorentz et al., 2005; Sellge et al., 2014).