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REVIEW

Intrinsic Gastrointestinal Macrophages: Their Phenotype and Role in Gastrointestinal Motility

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SUMMARY

This review focuses on the role of muscularis propria macrophages in gastrointestinal tract motility under both normal and pathologic conditions.

There is an increasing awareness of the role of macrophages in the regulation and maintenance of gastrointestinal function in health and disease. This work has proceeded in the context of an increased understanding of the complex phenotypic variation in macrophages throughout the body and has shown previously unidentified roles for macrophages in diseases such as gastroparesis, postoperative ileus, and inflammatory bowel disease. Opportunities for exploiting the phenotypic modulation of tissue resident macrophages have been identified as possible therapies for some of these diseases. In addition, macrophages are an established component of the innate immune system and can respond to variations and changes in the intestinal microbiome and potentially mediate part of the impact of the microbiota on intestinal health. We reviewed the latest work on novel concepts in defining macrophage phenotype, discuss possible mechanisms of action for tissue-resident macrophages in the gut, address the significance of microbiome effects on macrophage phenotype, and review the known and possible roles of macrophages in motility disorders of the gastrointestinal tract. *(Cell Mol Gastroenterol Hepatol 2016;2:120–130; http://dx.doi.org/10.1016/j.jcmgh.2016.01.003)*

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The extraordinary cellular complexity of the gastrointestinal (GI) tract is a reflection of the diverse roles of the organ. From an immune perspective, this means that there are complex interactions between multiple cell types that differ along the length as well as across the thickness of the wall of the GI tract. These interactions are constantly changing with development, age, alterations to the luminal content, and disease. This review is about one cell type, the macrophages, that within the GI tract represent the largest population of macrophages in the body[1,2] and can be involved in multiple GI functions. We review recent discoveries with respect to the complex phenotypic variations in macrophages and how these are modified in health, development, and disease. We refer to cells in all layers of the wall of the GI tract as shown in Figure 1, which shows the sources and destinations of macrophages in the GI tract. The primary focus is on macrophages residing in the muscularis propria and the consequences of their phenotypic changes on GI motility. Because there already are extensive reviews in the literature on the origins and roles of macrophages in the mucosa and submucosa,[3,4] the functions and properties of those macrophages are discussed in less detail and in the context of disturbances to GI motility or in comparison with the functions and properties of muscularis propria macrophages.

Macrophages in the Gastrointestinal Tract: Where Do They Come From?

Many types of cells of myeloid lineage including macrophages, but also microglia in the brain, Kupffer cells in the liver, and bone osteoclasts, are considered to be tissue resident.[5] The source and maintenance of these cells are either ongoing population from circulating monocytes with varying rates of turnover or in some cases by population from yolk sac–derived progenitors and maintenance by self-renewal. Microglia represent a well-defined example of these self-renewing, stable, tissue resident cells.[6] Renewal of resident macrophages is also from macrophage precursors that develop in the bone marrow, then enter into the blood stream as mature monocytes, and, finally, migrate into a specific tissue where they develop into a resident macrophage population.[7] In many tissues they develop from primitive macrophages existing in the yolk sac or fetal liver and are maintained independently from bone marrow–derived monocytes in the steady-state condition.[4,8–10] However, by

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Abbreviations used in this paper: BMP, bone morphogenetic protein; CCR2, C-C chemokine receptor type 2; CD206, mannose receptor C, Type 1 aka MRC1; CSF1, colony-stimulating factor 1; CSF2, granulocyte monocyte colony stimulating factor; CX3CR1, chemokine receptor 1; GI, gastrointestinal; HO-1, heme oxygenase 1; IBD, inflammatory bowel disease; ICC, interstitial cells of Cajal; IL, interleukin; iNOS, inducible nitic oxide synthase; Ly6C, lymphocyte antigen 6C; MCP1, monocyte chemoattractive protein-1; NOD, nonobese diabetic mouse; op/op, osteopetrotic mouse; TGF, transforming growth factor; TGM2, transglutaminase 2; TNBS, 2,4,6-trinitrobenzene sulfonic acid; TNF, tumor necrosis factor.

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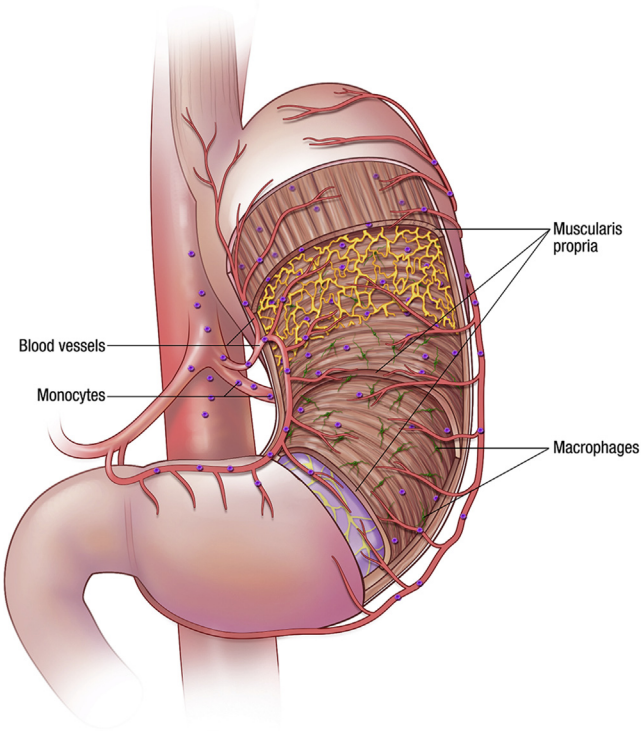

Figure 1. Distribution of resident macrophages in the gastric muscularis propria. Circulating monocytes are recruited to the tissue where they become macrophages influenced by the local environment.

tracking macrophage development from birth to adulthood in the mucosa and lamina propria, it was observed that although primitive macrophages are present in the neonatal intestinal mucosa and lamina propria they are not maintained in adulthood.[11,12] This important finding suggests that in contrast to other tissues, macrophages that reside in the GI mucosa and lamina propria of adult mice are replaced continuously by blood monocytes and that yolk sac–derived macrophages are short-lived and/or rare. This is reasonable given that mucosal and lamina propria macrophages are thought to monitor and respond to multiple factors at the interface between the organism and the luminal environment, and that these factors and responses are variable and can change rapidly. The resident macrophages of the muscle layers have not been studied in as much detail. These cells are abundant throughout the GI tract and express a limited number of phenotypic markers of activation.[13–17] It is clear that monocytes can be detected in the muscularis propria layers of control mice, an immune cell infiltrate derived from monocytes can be detected after inflammation in animal models,[18,19] and that varying numbers of macrophages can be identified by mannose receptor, C Type 1 (CD206, MRC1) immunoreactivity in human gastric muscularis propria.[20] Our recent data have indicated that population of the gastric muscularis propria in macrophage-depleted, osteopetrotic (op/op) mice can occur by monocyte invasion and can produce both CD206-positive and CD206-negative macrophages. These studies all identified macrophages that express markers that are not present on resident macrophages in healthy, GI smooth muscle, such as those in the GI tract of nonobese diabetic (NOD) mice when they are not diabetic.[21] Thus, muscularis propria macrophages are derived at least partially from monocytes and it remains to be determined whether some resident macrophages are the equivalent of microglia in the brain, derived from yolk sac progenitors and sustained by self-renewal. Determining the fate and source of all macrophages in the muscularis propria is an important research opportunity for the future.

Macrophage Phenotypes in Healthy Tissues

The phenotype of macrophages in healthy tissues appears to be determined in part by the original monocyte progenitor from which the macrophages were derived as shown in Figure 2 and Supplemental Poster. This is shown most clearly in op/op mice, which show reduced numbers of macrophages in most tissues. Monocyte development and survival depends on colony-stimulating factor 1 (macrophage) (CSF1), and op/op mice have an inactivating mutation in the gene encoding CSF1.[15,22]

In mice, monocytes can be identified by CD115 immunoreactivity and can be divided into 2 different groups according to differences in lymphocyte antigen 6C (Ly6C) expression. $CD115^+$ $Ly6C^+$ monocytes are associated with an inflammatory phenotype and differentiation into conventionally activated, proinflammatory M1 macrophages or inflammatory dendritic cells when they enter tissues. In the GI mucosa and lamina propria, $Ly6c^{hi}$ monocytes develop an intermediate phenotype once inside the tissue, defined as chemokine receptor 1^{int} ($CX_3CR_1^{int}$) before they differentiate into mature macrophages.[12,23] It takes 4–5 days for monocytes to acquire the phenotype of resident mucosal and lamina propria macrophages characterized by the expression of F4/80, CD64, major histocompatibility complex II, CD11c, and CX_3CR_1, and are associated with a slower rate of cellular turnover.[12] CX_3CR_1 expression is associated with a signature cytokine profile. $CX_3CR_1^-$ macrophages are characterized by high levels of proinflammatory cytokines such as interleukin (IL)6, inducible nitric oxide synthase (iNOS, NOS2), IL1β, and tumor necrosis factor (TNF)α.[12,24] In contrast, $CD115^+$, $Ly6C^-$ monocytes do not express inflammatory markers, are long-lived, and contribute to the resident macrophage population in GI mucosa.[25,26] $Ly6C^{lo}$ monocytes appear to be a precursor of a subset of resident $CX_3CR_1^+$ macrophages that are characterized by lower levels of C-C chemokine receptor type 2 (CCR2) and CD62L (L-selectin), and have an anti-inflammatory signature with increased levels of IL10 and heme oxygenase-1 (HO-1) and CD206.[12] These $Ly6C^{lo}$ monocytes are a possible alternative to yolk sac progenitors as a source of resident macrophages in GI muscularis propria, but this has not been tested and it should be noted that the resident macrophages in the healthy muscularis propria express very low levels of HO-1 and CD206 in, for example, nondiabetic NOD mice.[21] Furthermore, flow cytometry and immunohistochemistry indicate that macrophages in healthy mouse intestinal muscularis propria are a homogeneous population of major histocompatibility complex II^{hi}, $CD11c^{lo}CD103^+$ $CD11b^+$