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REVIEW

Heterogeneity across the murine small and large intestine

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Abstract

The small and large intestine of the gastrointestinal tract (GIT) have evolved to have discrete functions with distinct anatomies and immune cell composition. The importance of these differences is underlined when considering that different pathogens have uniquely adapted to live in each region of the gut. Furthermore, different regions of the GIT are also associated with differences in susceptibility to diseases such as cancer and chronic inflammation. The large and small intestine, given their anatomical and functional differences, should be seen as two separate immunological sites. However, this distinction is often ignored with findings from one area of the GIT being inappropriately extrapolated to the other. Focussing largely on the murine small and large intestine, this review addresses the literature relating to the immunology and biology of the two sites, drawing comparisons between them and clarifying similarities and differences. We also highlight the gaps in our understanding and where further research is needed.

Key words: Large intestine; Small intestine; Epithelial; Immune; Microbial

Core tip: The small and large intestine of the gastrointestinal tract (GIT) have evolved to have different functions and have a distinct anatomy, biology and immunology. Despite this, findings from the small intestine are often inappropriately attributed to large intestine and *vice versa*. The importance of these biological differences is underlined when considering that different regions of the GIT are associated with different infections and pathologies. This review addresses the literature relating to the small and large intestine – clarifying the similarities and differences between the two sites. We also highlight the gaps in our understanding where further research is needed.

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INTRODUCTION

The gastrointestinal tract (GIT) is the largest mucosal surface in the body; approximately 8.5 m long in humans and 30 cm long in mice, with approximately 80% of this compromising of the small intestine[1-3]. The duodenum, jejunum and ileum make up the anterior to posterior structure of the small intestine, with the caecum, colon

and rectum comprising the large intestine. As a consequence of its main role in food processing and nutrient extraction, the mucosal surface of the intestine is at high risk from attack by pathogens that contaminate the host' s food. In addition to thwarting attack from pathogens, the intestine is also home to a large number of commensal microbes (the microbiome) to which tolerance must be maintained. Therefore, it is paramount that the local immune system strikes an effective balance between tolerance and immunity. The large and small intestine are anatomically and functionally different and should be considered as two separate immunological sites which is significant when considering the aetiology and pathogenesis of intestinal tract diseases. Regarding infection, the small and large intestine are susceptible to different pathogens; whipworm species such as *Trichuris trichuria* (human) or *Trichuris muris* (*T. muris*)(mouse) and *Clostridium difficile* colonise the large intestine whereas *Ancylostoma duodenale* (human), *Ascaris lumbricoides* (human), *Heligmosomoides polygyrus* (mouse), *Trichinella spiralis* (human and mouse) and *Norovirus* infect the small intestine. Similar distinctions are seen in allergy and autoimmunity; Coeliac disease is restricted to the small intestine and ulcerative colitis to the large intestine whereas Crohn's Disease affects any region of the gastrointestinal tract (GIT). Moreover, cancer of the small intestine is rare whereas colon cancer is more common (2.4 patients per 100000 compared with 54 per 100000 respectively)[4]. Appreciating the immunological heterogeneity between the small and large intestine can provide answers to why this spectrum of disease along the GIT is apparent. Furthermore, a greater understanding of the cellular diversity within the GIT aids in the development of region-specific therapeutic targets for inflammatory bowel diseases and allergy. This review aims to highlight the differences and similarities between the small and large intestine of mice discussing both architectural and immune components.

INTESTINAL EPITHELIAL CELLS

The large and small intestine are lined with a single layer of columnar epithelial cells that are linked *via* complexes of junctional proteins and desmosomes creating a sealed yet dynamic barrier[5]. Enterocytes and enteroendocrine cells are found throughout the GIT and are involved in nutrient and water absorption[6] and hormone production[7]. The base of the crypts in the GIT contain undifferentiated stem cells from which progenitor cells are derived[8-10] and develop into any of one of four major differentiated epithelial cell types; enterocytes, Paneth cells, goblet cells, enteroendocrine cells[6]. Leucine-rich repeat-containing G protein-coupled receptor 5 stem cells are intermingled with Paneth cells in the small intestine supplying necessary signals for the stem cell niche[11]. However, there are distinct cellular features between small and large intestinal epithelial cells (EC) that have evolved out of the need to perform different digestive processes. Small intestine EC play a critical role in nutrient absorption that is reflected in their unique structure. In addition to the small intestinal epithelium being folded in such a way to create the crypts of Lieberkühn, it is further adapted with finger-like projections called villi thus collectively increasing the surface area for maximal nutrient absorption (Figure 1). Furthermore, villous EC are striated with numerous actin-rich microvilli that further maximise their surface area. In contrast, the large intestine, which is primarily involved in water absorption and fermentation, has EC which lack villi.

Although the primary role of the villi is nutrient absorption, they are also intimately associated with immune cells (described below), highlighting their role in immunity. The different functions of the small and large intestine place different demands on the immune system. For example, most protein antigens are taken up in the small intestine by specialised cells including Microfold or "M" cells. M cells transcytose luminal particulate antigens, effectively passing them onto underlying immune cells. M cells are most abundant overlying the Peyer's patches of the small intestine but have also been described in the villous epithelium[12]. In the large intestine, M cells are less numerous and are usually associated with isolated lymphoid follicles and colonic patches[13].

ANTI-MICROBIAL PROTEINS

In addition to processing antigens, the intestinal epithelium plays a direct role in innate mucosal defence *via* production of anti-microbial peptides (AMPs). The requirement for different types of AMPs varies along the GIT reflecting the need to respond to different commensal and pathogenic microbes that colonise the GIT[14-17]. Paneth cells, a specialized lineage of cells unique to the small intestine, are a major source of AMPs including α-defensins (also called cryptdins in mice)[18], lysozyme, ribonucleases [such as angiogenin 4 (ANG4)], secretory phospholipase A2[14,16,17] and C-type lectins [such as the regenerating islet derived protein (REG3) family][19,20]. AMPs are thought to act as mediators in host defence against pathogens[21] and in shaping the microbiome composition for the maintenance of homeostasis[14,22]. AMPs such as REG3γ and REG3β promote spatial segregation of microbial populations from the epithelial surface of the small intestine[15,20]. AMPs also help shape microbial diversity and thus may contribute to the relatively low bacterial burden in the duodenum compared with the large intestine[23]. In addition to the production of AMPs, Paneth cells may directly recognise pathogens *via* pattern recognition receptors enabling them to initiate innate immune responses[17,20,23,24].

The unequal distribution of Paneth cells along the GIT, however, is not the sole factor participating in the differential arsenal of antimicrobial proteins between the small and the large intestine. Enterocytes along the entire GIT can be induced to express a distinct group of AMPs[16,17]. Enterocytes in the small intestine stimulate the production of REG3γ and REG3β[19,20],

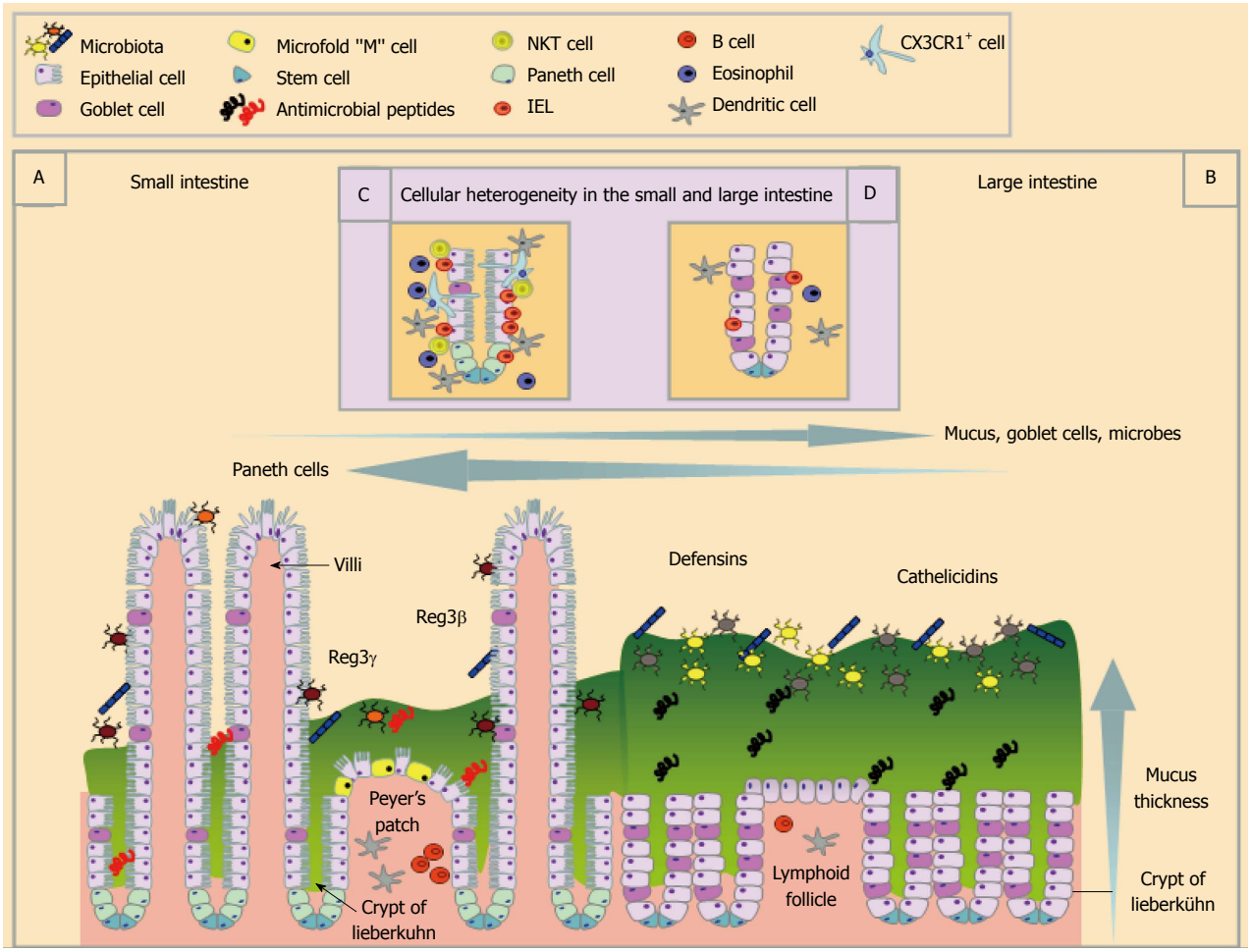

Figure 1 Schematic representation of the structural and cellular heterogeneity within the small and large intestine during homeostatic conditions. The small (A and C) and large (B and D) intestine differ greatly in their structure and cellular composition. The small intestinal epithelium is folded to create crypts of Lieberkühn, has finger-like projections called villi and epithelial cell possess striated microvilli (A) whereas the large intestine (B) has crypts and lacks villi. The small intestine has Peyer's patches, the main site of Microfold or "M" cells that transcytose luminal particulate antigens that are rare in the larger intestine. Both the small and large intestine are covered by mucus, which is much thicker in the large intestine (B) than in the small intestine (A). The large intestine houses the largest and most diverse microbial populations of the two sites (B). Anti-microbial peptides are also differentially expressed along the gastrointestinal tract. The distribution of immune cells also differ in the small and large intestine (inset C and D) with Natural killer T cells, Intraepithelial lymphocytes (IEL), eosinophils and dendritic cells found in the highest numbers in the small intestinal epithelium under steady state conditions. Cell populations are defined in the key.

whereas those in the large intestine drive the synthesis of β-defensins[25] and cathelicidins[26]. As well as differences between the large and small intestine, within the large intestine there is also a different AMP profile between the proximal and distal gut which may be related to different microbial composition[27].

Goblet cells exhibit a non-homogenous distribution along the intestinal epithelium, and are more abundant in the large intestine. They release a panel of bioactive compounds including mucins, AMPs [such as resistin-like molecule β (Relmβ; also known as FIZZ2)[28], ANG4[29], REG3γ and REG3β[27]] and trefoil peptides[30] that further contribute to innate immune defence. REG3γ expression is minimal in the large intestine compared to the small intestine[15,20]. In contrast, Relmβ is expressed mainly in the large intestine and only a small amount is present in the normal terminal ileum and there is no Relmβ expression in the other areas of the small intestine[28]. Relmβ may exert a function analogous to REG3 proteins in the small intestine, keeping bacteria at a distance in the large intestine[15]. The prevalence of different AMPs at distinct sites of the GIT is due to both the distinctive primary cellular source but also due to different expression profiles of the same cells (enterocytes or goblet cells) in the different regions.

Alterations in microbial composition, due to physiologic[27,31] or pathologic states[32,33], as well as alterations in bacterial-epithelial interaction[27] can also change AMP expression patterns. The intricate cross talk between AMP expression and the microbiome generates a feedback loop, where AMPs can influence microbiome structure and microbes themselves can direct AMP synthesis[14,15]. Strikingly, short chain fatty acids, products of bacterial fermentation of dietary fibres and/or host mucin glycans can drive the expression of AMPs on colon epithelial cells[34], emphasizing the impact of bacterial metabolites on AMP site-specific expression. AMPs are concentrated within the mucus layer overlying the intestinal epithe-

lium[35] (Figure 1).

MUCUS AND MUCINS

Mucus functions as a physical, chemical and immunological barrier and is enriched in mucin glycoproteins[36], nonspecific AMPs[37] and secretory immunoglobulin A (sIgA) and G (IgG)[36]. Mucins are the major structural components of mucus, which comprises a family of 17 mucins[38] and are produced in the GIT as either membrane bound or secreted. In the small and large intestine, the mucus layer consists of secreted MUC2 and smaller amounts of transmembrane MUC1, 3A/B, 4, 12, 13, 15 and 16[36]. In the large intestine the mucus layer is approximately four-fold thicker than that of the duodenum and jejunum[39].

The mucus barrier consists of two layers; a thinner inner "firm" mucus layer, which is physically difficult to dislodge and is considered devoid of bacteria, and a thicker outer "loose" mucus layer, in which anaerobic microbiota may reside[40]. There is a debate in the literature regarding the presence of a firm mucus layer in the small intestine. Atuma *et al*[39] have shown the existence of a firm and loose mucus layer throughout the gut (including both the small and large intestine) with the mucus layer of the large intestine characterized by a more substantial layer of "firm" mucus. However, recent findings indicate that MUC2 forms a single soluble mucus gel in the small intestine, which is not attached to the epithelium and is penetrable to bacteria[41,42]. The absence of a firm organized mucus in the small intestine may allow direct antigen sampling by dendritic cells (DCs) conditioning them to a tolerogenic state, highlighting the importance of MUC2 in gut homeostasis[42]. The novel finding that MUC2 alone or coupled with bacterial antigens can deliver immunoregulatory signals both to underlying DCs and intestinal ECs advances the concept of the role of mucus as a barrier. Despite the recent advances on mucus research, there is much we do not know about the organization of mucus network in the small and large intestine and how AMPs may modulate it. Recent evidence that Reg3γ affects the distribution of mucus in the ileum but not in colon[43] raises important questions regarding the effects of AMPs on mucus structure given the unequal distribution of AMPs along the GIT.

A distinguishing feature of mucins is their heavy glycosylation, which is determined by the expression pattern of glycosyltransferases[36,41]. A disparity in mucin glycan content is evident between different sites of the GIT[44] and, in fact, in adjacent crypts or even in the same crypt[36]. Sialylated and sulfated glycans dominate the small intestine, whereas fucosylation is prevalent in the large intestine[44]. The mucin glycosylation profile may affect bacterial composition, providing potential adhesion sites[45] as well as bacterial energy sources[46]. Mice deficient in fucosylation of mucins exhibit an altered microbial structural configuration and expression profile in a manner dependent on the availability of diet-derived polysaccharides[47]. Thus, mucus functions not only as a barricade of enteric microorganisms, but also plays a role in the determination of bacterial composition alongside AMPs and sIgA.

The essential role of mucins in GIT health is demonstrated by reports showing the severe pathologies that develop in MUC-deficient animals[48-52]. Furthermore, *de novo* induction of MUC5AC in the mouse large intestine plays a key role in resistance to intestine nematode infection[53]. The mucin barrier responds dynamically to microbial signals and the immune response with an impact on mucin biosynthesis rate, secretion and glycosylation profiles[36,54,55]. Further research on the dynamic mucin changes during infection and inflammation is warranted to shed more light on mucus function and the potential for different roles in the small and large intestine.

GIT MICROBIOTA AND MICROBIOME

The microbiota is the community of commensal, symbiotic, and pathogenic microorganisms that reside within the GIT with the combined genetic material of these microorganisms comprising the microbiome. The microbiota consists of approximately 500-1000 bacterial species[56-59] yet represents a small fraction of the known bacterial phyla. The most abundant phyla are Bacteroidetes and Firmicutes; however, species belonging to other phyla such as Proteobacteria and Actinobacteria are also encountered[22,60,61]. The GIT microbiota increases longitudinally along the GIT[59,62] with 10^{10}-10^{11} bacteria per gram of intestinal contents in the large intestine but only 10^{3}-10^{4} bacteria per gram of intestinal content in the duodenum and jejunum[63]. The bacterial density and abundance also increases transversely from the mucus to the lumen[62]. Additionally, the composition of the gut microbiome varies along the length of the gut depending on the intestinal site and specific niches[61,64]. For example, Firmicutes and, more specifically the families Lachnospiraceae and Ruminococcaceae are more prevalent at mucosal surfaces of the large intestine compared to the lumen[65]. The reasons for these differences include the slow transit time, changes in oxygen tension along the GIT, and the action of secreted factors including gastric acid and bile salts in the small intestine[66-68]. Moreover, the microbiota of the small intestine is adapted to process simple carbohydrates whereas large intestinal microbial communities efficiently degrade complex polysaccharides[69]. Among the multiple factors that can sculpt the GIT microbial architecture, diet and metabolic requirements have a major role in the microbiome differences throughout the GIT[70-72]. Interestingly, ileal microbiota display a relative instability over time in humans[73], whereas most bacterial strains of the large intestine reside for most or a lifetime[74]. Data in mice are lacking regarding the temporal variability of microbial populations in different sites.

The disparity in microbial communities inhabiting different niches of the gut is reflected by disparate mucosal

immune responses, which are time and region dependent. Immune tolerance in response to the gut microbiome is established earlier in the large intestine compared with the small intestine[15]. Also, different bacteria strains can have different effects on host immune responses in different parts of the gut[75]. Administration of the probiotic *Lactobacillus salivarius* UCC118 elicits regulatory T cell responses in the small intestine, whereas, it activates inflammatory responses in the large intestine[75].

Differences in bacterial colonisation of the GIT impact on functionality in three ways: structural, protective, and metabolic. Due to the larger microbial load of the large intestine, there is likely to be a greater pressure on maintaining a structural barrier with a thicker mucus layer and abundant goblet cells[40]. As the presence of a firm mucus layer in the large intestine prevents direct contact between the microbiome and EC[40] then bacteria/epithelial cell crosstalk may be more prevalent in the small intestine. However, there may be non-cognate interactions with epithelial cells that are mediated *via* bacterial products or secretions which given the greater density of bacteria in the large intestine may be of greater significance in this region of the GIT. Isolated large intestine EC can distinguish between different commensal bacteria by secreting different chemokines[76] and thus may contribute directly to homeostasis. In terms of protection, the GIT microbiome can resist colonisation by pathogens by direct competition for nutrients and space and/or *via* production of microbicidal compounds[32]. The microbiome and its associated metabolites[77] play additional roles in resistance against infection by for example, priming immune cell function[78-80] and by promoting the development and/or regulation of innate lymphoid cells (ILCs)[62,81,82] and, specifically in the ileum, Th17 cells[83-85]. Conversely, the immune system also helps shape the composition of the microbiome[86]. It can be inferred, therefore, that changes in the microbiome along the GIT contribute to differences in the types and function of immune cells throughout the GIT.

IMMUNE CELLS OF THE GIT

The GIT contains the largest immune system in the body and is densely populated with many different immune cells. The greatest density of immune cells resides in the small intestine, which is perhaps not surprising given its absorptive function. Throughout the GIT differences in the make-up and functionality of immune cells are observed with many aspects of their function, particularly in the large intestine, not fully understood.

DCS AND MACROPHAGES

Mononuclear phagocytes can be subdivided into macrophages or dendritic cells, however, there has been extensive debate as to what distinguishes the two[87,88]. The extent of macrophage and DC heterogeneity within the large and small intestine is considerable (Table 1 and Figure 2), presumably reflecting the anatomical and physiological differences in the two sites. Data to date shows that DCs are more abundant in the small intestine. Nevertheless, DCs in the large intestine are functionally important to intestinal health as their absence or depletion can result in severe pathology and tissue destruction[89].

DCs can be classified as conventional, inflammatory or plasmacytoid based upon the differential expression of key surface markers and their functional characteristics. There are clear regional differences of DC subtypes throughout the GIT, which may be of functional significance. Conventional lymphoid resident DC ($CD11c^{high}$, $MHCII^{high}$ $CD64^{-}$)[90] do not migrate or present antigen to T cells within their local environment and can be grouped into $CD8\alpha^{+}$, $CD11b^{+}$ and $CD8\alpha^{-}CD11b^{-}$ DCs which within the small intestine are located in Peyer's patches[91,92]. In the lamina propria (LP) of the small intestine $CD11b^{+}CD8\alpha^{-}$ DCs are the most abundant[93]. $CD8\alpha^{-}CD11b^{-}$ DCs have been identified in regions of the large intestine[94], although $CD11c^{hi}CD11b^{-}CD8\alpha^{+}$ lymphoid DCs have not been identified in homeostasis[93,94]. Furthermore, whereas in the small intestine, DC are readily observed near the epithelium and are able to rapidly respond to damage or infection, in the large intestine DCs are rare in the LP and need to be recruited to the site of infection or injury[94,95].

Interestingly within the small intestine, approximately 80% of the $CD11c^{hi}$ LP DC express CD103[93] which have been shown to induce $FoxP3^{+}$ Treg development[96,97] and also the up-regulation of gut homing receptors on lymphocytes which is in part mediated by retinoic acid[98-101]. Although this function was originally thought to be unique to DCs of the small intestine, DCs in the large intestine can also induce expression of the GIT homing receptor $\alpha4\beta7$ on T cells[102]. To add further complexity, $CD103^{+}$ DCs can be divided into $CD103^{+}$ $CD11b^{+}$ and $CD103^{+}$ $CD11b^{-}$ subtypes with the latter being more abundant in the large intestine[103]. Conventional $CD103^{+}$ $CD11b^{+}CD8\alpha^{-}$ DC have a migratory phenotype and are thought to sample antigen in the small intestine under steady state conditions and contribute to immune tolerance. They are thought to lack expression of the macrophage markers CX3CR1 (Fracktalkine receptor) and F4/80 and are rare in the steady state large intestine[95].

The behaviour of monocyte-derived inflammatory DCs appears to be comparable in both the small and large intestine. They accumulate in the large and/or small intestine in infection[104] and inflammation[105], for example in T cell-mediated colitis and *Toxoplasma gondii* infection. In the small intestine plasmocytoid $B220^{+}$ $CD11c^{intermediate}$ DCs are found in the LP in relatively low numbers but higher than that seen in the large intestine where they primarily reside in lymphoid follicles[94], representing less that 5% of DCs.

The identity of cells expressing CX3CR1 and their functional significance is again controversial. In the murine small intestine and in particular the jejunum, $CX3CR1^{+}$ cells can produce transepithelial dendrites that extend through the epithelial barrier and directly sample

Table 1 Immune cell populations within the small and large intestine

Cell type	Small intestine			Large intestine	Ref.
Dendritic/macrophage Cells					
Conventional DCs ($CD11c^{high}$ $MHCII^{high}$ $CD64^{-}$)					
$CD11b^{-}$ $CD8\alpha^{+}$	Yes. Peyers Patches (PP)			Not readily detected but have been identified after the use of Flt3 ligand	[93]
$CD11b^{+}$ $CD8\alpha^{-}$	Yes. PP, Lamina Propria (LP), and express CD103)			Yes. Isolated Lymphoid Follicles (ILF) and Colonic Patches. LP but scarce	[91,92]
$CD11b^{-}$ $CD8\alpha^{-}$	Yes. PP			Unknown	[91,92,94]
$CD103^{+}$	Yes			Yes. $CD103^{+}CD11b^{-}$ are more abundant	[91,92]
Monocyte derived DCs					
$Gr1^{+}$ $CD11c^{+}$ plasmacytoid DCs	Yes. Upon inflammation			Yes Upon inflammation	[104,105]
CD11cintBB20^{+} plasmacytoid DC	Yes. Small populations in LP			Yes ILF but rare	[93,95]
$CD11b^{+}$ $F4/80^{+}$	Yes. Intraepithelial lymphocytes (IEL) and lamina propria lymphocytes (LPL)			Mainly LPL, IEL are scarce	[110,193]
Macrophages					
$CX3CR1^{+}$	Yes Production of transepithelial identified. Higher frequencies in the jejunum. Fewer in ileum			Yes Production of transepithelial dendrites uncertain	[95,106-108,194,195]
Other innate cells					
Eosinophil	High numbers in steady state located below epithelium and in LP. Highest numbers are found in duodenum. High numbers of $CD22^{+}$ eosinophils			High numbers in steady state located below epithelium and in LP. Low numbers of $CD22^{+}$ eosinophils	[130-133,137,196]
Basophils	LP following infection, draining lymph node			Draining lymph node	[121-123]
Mast cells	Mucosal mast cells located close to the epithelium			Mucosal mast cells located close to the epithelium	[140]
NK cells	IEL and lymph nodes (LN)			IEL unknown, LN	[149,197]
NKT cells	IEL			IEL, LPL	[189,191,192]
Innate lymphoid cells	Nuocytes: Epithelium 0.2% of total cells and mesenteric lymph node (MLN)			Unknown	[151]
	Innate type 2 helper (Ih2): MLN peritoneum			Unknown	[153]
	Multipotent progenitor (MPP) type2: PP, MLN			Caecal patch	[155]
	Natural helper cell: fat associated lymphoid cluster in helminth infection			Unknown	[198]
T cells	1 T cell per 5-10 epithelial cells			1 T cell per 40 epithelial cells	[176]
IEL cells					
	Proximal	Mid	Distal		[199]
αβ T cells	59%	60%	78%	64%	
DN	1%	1%	1%	20%	
CD4	6%	7%	15%	7%	
CD8αα	43%	32%	20%	58%	
CD8αβ	46%	54%	57%	12%	
gd T cells	41%	40%	22%	36%	
DN	15%	17%	17%	69%	
CD4	0.15%	0.2%	0.3%	0.2%	
CD8αα	83%	82%	82%	30%	
CD8αβ	0.3%	0.5%	0.4%	0.2%	
LPL cells					
Th17	10%-15% of $CD4^{+}$ cells			2%-3% of $CD4^{+}$ cells	[83]
Regulatory T cells	50% of regulatory T cells are Tr1-like cells, 50% are $FoxP3^{+}$ cells			Almost devoid of Tr1-like cells and 90% of regulatory T cells are $Foxp3^{+}$	[182]
B cells					
IgA^{+}	Yes LP and in Peyer's patches			Found in small numbers	

DCs: Dendritic cells; NK: Natural killer; NKT: Natural killer T.

luminal contents[106-108]. However, the phenomenon of transepithelial dendrites in the large intestine may be a rare or transient event[95]. It was originally thought that these cells were static in the epithelial layer although more recent data has suggested that these $CX3CR1^{hi}$ cells are also capable of migration[109]. Recently it has been demonstrated that $CX3CR1^{+}$ cells are a heterogeneous population expressing varying levels of CX3CR1[90] calling for a re-evaluation of the data surrounding $CX3CR1^{+}$ cells, in particular, analysis of the expression levels of CX3CR1 and CD64 to distinguish between macrophages and DC.

In addition to CX3CR1, macrophages can be further defined by expression of CD11b, F4/80 and CD64[90]. In the large intestine $CD11b^{+}F4/80^{+}$ macrophages predominantly reside within the LP and are rarely found associated with the epithelium in naïve animals[110] whereas,

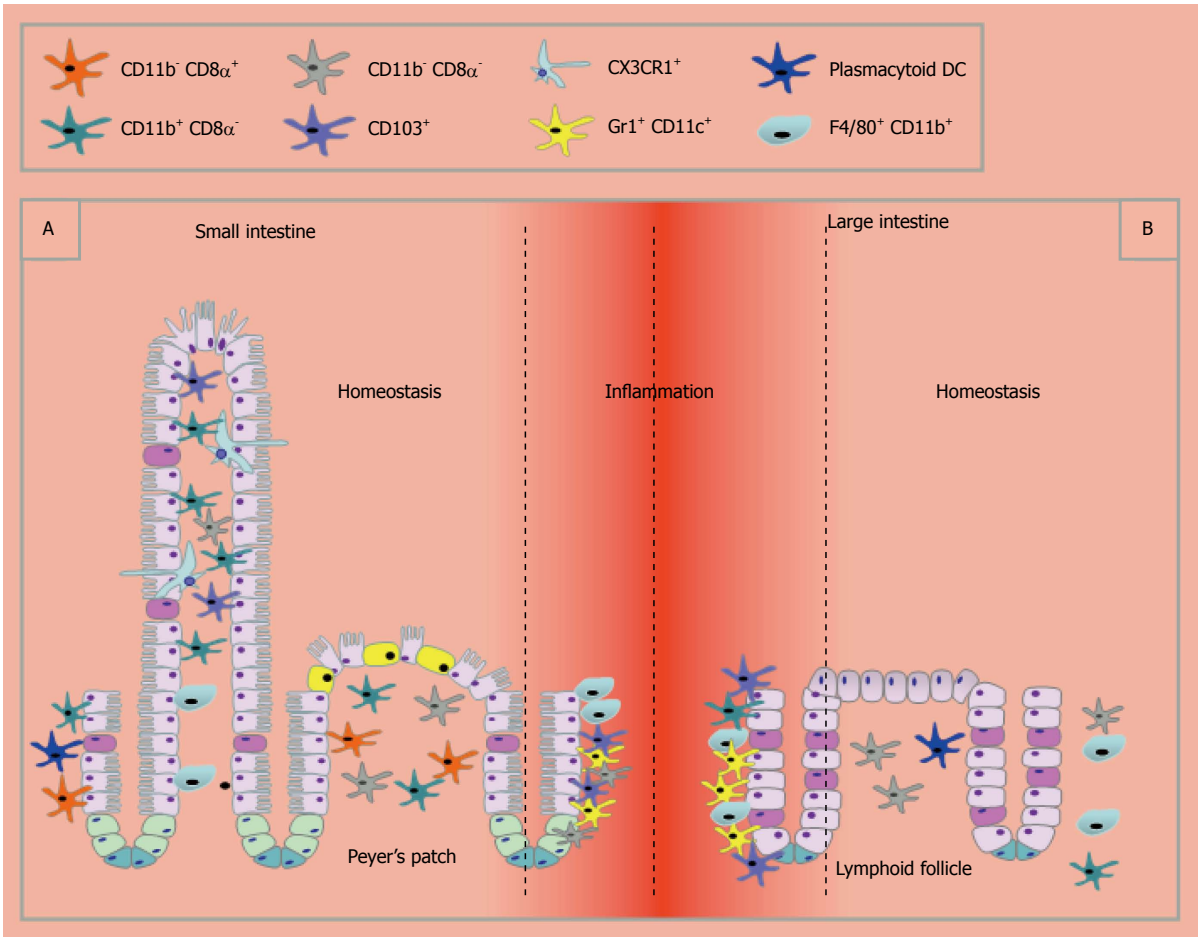

Figure 2 Schematic representation of the distribution of dendritic cell and macrophage subset in the small and large intestine under homeostatic conditions and upon inflammation. In homeostasis dendritic cells (DCs) and macrophages are found in close contact with the epithelium in the small intestine (A) whereas in the large intestine they are rare and in the LP (B) and are recruited in response to inflammatory stimuli. Within the small intestine lymphoid resident DC ($CD11c^{high}$, $MHCII^{high}$ $CD64^{-}$) can be grouped into $CD8\alpha^{+}$, $CD11b^{+}$ and $CD8\alpha^{-}CD11b^{-}$ DCs, which are located in Peyer's patches. In the lamina propria (LP) of the small intestine $CD11b^{+}CD8\alpha^{-}$ DCs predominate. $CD8\alpha^{-}CD11b^{-}$ DCs have been identified in regions of the large intestine, including the ILFs, but $CD11b^{-}CD8\alpha^{+}$ DCs are rarely found during homeostasis. Plasmacytoid $B220^{+}$ $CD11c^{intermediate}$ DC are present in very low numbers in the LP of the small intestine and ILFs of the large intestine. In the small intestine $CX3CR1^{+}$ cells can produce transepithelial dendrites that extend through the epithelium to directly sample luminal contents. This has not been demonstrated in the large intestine during homeostasis. In addition to CX3CR1, macrophages can be further defined by expression of CD11b, F4/80 and CD64. Upon inflammation, $Gr1^{+}$ monocyte-derived inflammatory DCs accumulate in both the small and large intestine.

in the small intestine macrophages are found closely associated with overlaying enterocytes[87]. In the resting mouse colon, most $F4/80^{+}CD64^{+}CD11b^{+}$ macrophages express unusually high levels of CX3CR1, but there is also a significant population of $CX3CR1^{int}$ cells that expands preferentially in inflammation. It has recently been determined that these cells represent stages in a single differentiation continuum from lymphocyte antigen 6C monocytes to mature $CX3CR1^{hi}$ macrophages[90,111]. Importantly, there are no known differences in macrophage subset proportions between the small and large intestines[111]. Macrophages exist in different activation states including classical and alternative, based upon the cytokines they are exposed to[112]. Alternatively activated macrophages have been shown to be important in small intestine pathogens such as the helminth *Heligmosomoides polygyrus*[113] but do not appear to play a direct role in the response to large intestine parasite *T. muris*[114]. Whether this contrast is due to the different helminths or a differential role in the small *vs* the large intestine is not known. It will be interesting to see if differences between the small and large intestinal monocyte/macrophage lineages become apparent as more research is done in this emerging area of research.

NEUTROPHILS

Neutrophils are an essential component of innate immunity and host defence. They initiate innate immunity as well as directly kill pathogens *via* the release of extracellular "traps"[115], contribute to inflammation by producing interleukin (IL)-17 and IL-23[116], and may act as professional antigen presenting cells in promoting Th1 and Th17 differentiation[115]. Neutrophils are rare in the intestine although their expansion in response to infection or injury is a hallmark feature of GIT diseases including inflammatory bowel disease (IBD)[117], colorectal carcinoma[118], coeliac disease and infection[119]. The microbiota

may play a role in neutrophil expansion in ulcerative colitis and infection[117,120]. Data on regional differences along the GIT are lacking. Given the importance of neutrophils in effector immunity and their prominence in chronic inflammatory conditions it would be important to know if there are regional or functional differences in the neutrophils along the GIT that are of relevance to mucosal immunity and injury.

BASOPHILS

Basophils are uncommon or absent in the small intestinal mucosa, although they accumulate in high numbers in the LP of the small intestine following *Nippostrongylus brasiliensis* (*N. brasiliensis*) infection[121]. Furthermore, they are recruited to the draining lymph node during helminth infections and have a role in the development of type 2 responses[122,123]. The presence of basophils in the large intestine is not known, although one study suggests a role for basophils in the expulsion of the large intestinal parasite *T. muris*[123] implying the possibility of their presence or (transient) recruitment to the large intestine[123]. Several studies also suggest that basophils have the ability to present antigen[123,124]. Given the potential importance of basophils both in potentiating type 2 immunity it would be interesting to determine whether there are differences in basophil function along the GIT.

EOSINOPHILS

Eosinophils have multiple roles including supporting plasma cell function[125], recruitment of DCs[126] and regulation of obesity[127] with the GIT containing the largest number of eosinophils in the body under steady state conditions[128,129]. Within the GIT the duodenum contains the largest population of eosinophils[130]. In both the small and large intestine eosinophils reside primarily in the LP and submucosa with some being detected in the villi of the small intestine[130]. Eosinophilia is seen in response to infection and in inflammation of both the large[131,132] and small intestine[133]. Circulating eosinophils are recruited to the GIT by different mechanisms with steady state recruitment to the large intestine dependent on I-CAM1[134] and small intestine recruitment involving $\alpha_4\beta_7$[135]. Additionally during inflammation, $\beta7$ and $\alpha_4\beta_1$ integrins are important in recruitment to the small and large intestine, respectively[136]. Eosinophil populations within the GIT can be distinguished phenotypically with $CD22^+$ eosinophils being most frequent in the jejunum and rarest in the large intestine[137]. The functional significance of these phenotypic variants is however not known although the increased frequency of eosinophils in the small *vs* the large intestine implies they may be of greater functional significance in this region of the GIT, at least in the steady state.

MAST CELLS

Mast cells are major effector cells in the immune response to infection, driving pro-inflammatory responses *via* the release of inflammatory mediators and recruitment of other immune cells[138,139]. They are long-lived cells and enriched at barrier surfaces including the skin and intestinal mucosa[138]. Mast cells are resident cells in both the large and small intestine and mastocytosis is often a feature of GIT infection and inflammation. Two types of mast cell have been identified in the murine small and large intestine based upon differential expression of mast cell proteases (MCP): Mucosal m-$MCP1^+$ and m-$MCP2^+$ cells that reside close to the epithelium and connective tissue mast cells that express mMCP4, mMCP5, mMCP6 and mMCP7 that are within the submucosa[140]. Mucosal mast cells produce lower levels of histamine and high amounts of cysteinyl leukotrienes compared with connective mast cells. Mast cells are critical cells in the expulsion of the small intestinal helminth *Trichinella spiralis*[141] whereas their role in resistance to the related large intestinal dwelling helminth *T. muris* infection is less clear[139,142] and presumably reflects functional differences between mast cells in the small and large intestine. Mast cells may also play a role in the pathophysiology of food allergy, cancer, irritable bowel syndrome and inflammatory bowel disease[143,144]. Mast cells may also contribute to altering intestinal permeability. It is known that mucosal mast cells can enhance epithelial barrier permeability in the small intestine[145] and mastocytosis is a feature of IBD, a hallmark feature of which is increased intestinal permeability. However, in the large intestine, which has a higher baseline epithelial resistance, a role for mast cells in mediating increased permeability is less likely[146]. Whether, these conflicting observations in permeability reflect the fact that mast cells are functionally different along the GIT or there are differences in mast cell subset function in homeostasis *vs* disease is not known, and is worthy of further investigation.

ILCS

ILCs are a newly identified member of the lymphoid lineage that are capable of producing type 1, type 2 and Th17 cytokines yet do not express any of the cell surface markers associated with other immune cell lineages[147,148]. Three groups of ILCs have been described based primarily upon their cytokine profiles.

Group 1 ILCs produce Interferon (IFN)-γ[147] with the prototypical member being Natural killer (NK) cells that comprise about 2% of small intestinal epithelia-associated lymphocytes in both lymphocyte-replete and -deficient mice[149]. Although NK cells increase in the draining lymph nodes in response to infection in the large intestine[149] their exact number and distribution in the large intestine are currently unknown. As well as NK cells IFNγ-producing non-cytotoxic ILC1s have been described which are more prevalent in the small intestine than the large intestine[150].

Group 2 ILCs produce Th2 associated cytokines following stimulation and require IL-7 for their development[147] and include natural helper cells, nuocytes and

Ih2 cells. However, it is not clear if these populations represent one cell type or are distinct and stable subsets of group 2 ILCs[147]. All of these ILCs are scarce in naive mice[151] therefore differences between intestinal regions under steady state conditions are hard to analyse. The ILC populations are elicited after small intestinal helminth infection[151-153] with, nuocytes being the predominant IL-13 expressing cell type within the mesenteric lymph node and small intestine after *N. brasiliensis* infection[151]. Similarly, in the large intestine, nuocytes are the main IL-13 producing cell type during experimental colitis[154]. Differences in the infection models driving inflammation however make it difficult to compare the populations directly following infection in the small and large intestine.

A multipotent progenitor like cell cell has been described which gives rise to cells of the monocytes/macrophage and granulocyte lineage[155]. These cells expand under the influence of IL-25 and are found within Peyer' s patches of the small intestine and the caecal patch of the large intestine[156]. In the small intestine these cells expand in response to *N. brasiliensis* infection and in the large intestine they expand in response to *T. muris*[156], and have been shown to have important roles in promoting Th2 cytokine responses to helminth infections in both the small and large intestine.

Group 3 ILCs produce IL-17A and/or IL-22[147] with the prototypical members being LTi cells. Recently, another subset of group 3 ILCs has been identified that is crucial for the IL-22-mediated innate immune response against intestinal bacterial pathogens including *Citrobacter rodentium*[157]. Depletion of these IL-22 producing cells resulted in systemic inflammation and bacterial dissemination which could only be rescued by exogenous IL-22[143]. This population is primarily located in the LP of the intestine being three times more frequent in the small intestine than the large intestine[157].

Based upon the experimental evidence obtained to date, ILCs may play an important role in GIT barrier defence and perhaps intestinal inflammation; however more work needs to be done in this newly identified population of cells and differences between the small and large intestine are still emerging.

B LYMPHOCYTES AND IGA

B cells play a key role in adaptive mucosal immune responses *via* antibody production. In the GIT, IgA secreting plasma cells represent the major pathway to blocking pathogen invasion. The GIT contains the largest number of IgA-producing plasma cells, which collectively produce and secrete 3-5 mg of antibody into the lumen each day[158]. IgA producing plasma cells are enriched in the LP of the small intestine but are found in smaller numbers in the large intestine LP (our unpublished observations). There are regional differences in the distribution of B cell follicles that contain IgA producing B cells. In the small intestine they reside within the Peyer's patches whereas in the large intestine they reside in isolated lymphoid follicles, although they are rarely seen, further emphasising differences in antigen presentation across the GIT. The mechanisms driving IgA production in the small and large intestine may overlap, particularly with regard to the role of the intestinal microbiota. In the small intestine the microbiota elicits IgA production, which leads to the development of gut-associated lymphoid tissue (GALT)[159,160]. Conversely, IgA can supress the growth of commensal bacteria[161]. In the large intestine, *Bacteroides acidifaciens,* a member of the microbiota has been shown to promote IgA production[162] but its not known whether this commensal drives GALT development.

T LYMPHOCYTES

In the GIT T cells are compartmentalised into the GALT, the LP, and the epithelium where they reside as epithelia-associated lymphocytes or intestinal intraepithelial lymphocytes (iIEL)[163]. Different mucosal T cell subsets reside in the different compartments of the GIT and there are striking differences in the distribution and function of iIEL subsets in the small *vs* large intestine iIEL, which has been extensively reviewed elsewhere[164-167] and will not be discussed in any detail here.

iIELs that express the integrin CD103[168-172] are in close contact with the intestinal epithelium and contribute to the maintenance of barrier integrity[170,173-175]. They are highly heterogeneous, comprising many different subsets that exhibit distinct regional differences throughout the GIT (Table 1). iIELs can be divided into two main groups, induced IELs (type A) that arise from conventional T cells and become activated in the periphery, and natural iIELs (type B) that develop in the thymus[164,165,176]. Both types of iIELs can be further divided based on the expression of the αβ or γδ T Cell Receptor (TCR) and on expression of CD4 and CD8 (Table 1). The distribution of iIELs in the small intestine is approximately one IEL per 5-10 epithelial cells *vs* one IEL per 40 epithelial cells in the large intestine[177,178]. A key difference between populations of iIELs throughout the GIT is the ratio between naïve and activated to memory IELs, with the small intestine containing a smaller proportion of naïve cells than the large intestine[179]. The function of iIELS are not fully elucidated however in addition to immune and cytotoxic roles, they play a vital role in small intestinal epithelial barrier maintenance[168] and defence by promoting epithelial tight junctions and Paneth cell antimicrobial production[180]. It is not known whether colonic iIEL have analogous functions to these small intestinal populations.

Compared to iIELs, the distribution of LP T cell subsets throughout the GIT is less well characterised. TCRαβ$^+$ CD4$^+$ cells are found in greater numbers in the LP of the both the small and large intestine in comparison to the epithelium[163]. In addition, classical CD4$^+$ Th subsets are found in the LP with Th17 and Treg cells present in high numbers[83]. Indeed the intestine has the highest levels of Th17, Th22 and FoxP3$^+$ cells in the body[181]. This enrichment of Th17 cells is particularly evident in the small intestine where approximately 10%-15%

of $CD4^+$ cells in healthy mice are $IL\text{-}17^+$ compared to 2-3% in the large intestine[182]. The GIT is also enriched in regulatory T cells (Treg) that can be subdivided into $Foxp3^-$ Tr1-like cells that produce large amounts of IL-10, and "natural" $Foxp3^+$ Treg. In the LP of the small intestine approximately 50% of regulatory T cells have a Tr1-like phenotype, in stark contrast to the large intestine, which is relatively devoid of Tr1-like cells. Instead, virtually all Treg cells in the large intestine are $Foxp3^+$ (89%) in comparison to 54%-58% of the Treg cells in the small intestine[183]. Indeed, it has become increasingly clear that mechanisms of tolerance differ greatly between the small and large intestine with differential induction of $Foxp3^+$ Tregs and Tr1 cells. Nevertheless, more detailed studies are needed to understand the contribution of dietary and bacterial antigens, antigen presenting cells and tissue resident cells in the induction of Tr1 and Treg cells and the differences between the small and large intestine[184].

In addition to differences in T cell composition throughout the GIT there are differences in the mechanisms of T cell homing to the gut. This is believed to be one of the key ways the tissue-specificity of T cells are maintained[181]. The adhesion molecules expressed by small intestine homing T cells are well characterised with LFA-1, $\alpha_4\beta_7$, $\alpha_E\beta_7$ (CD103) and CCR9 and retinoic acid playing an important role[100,101]. In contrast, the mechanisms involved in the recruitment of T cells to the large intestine are less well defined. It has been demonstrated that migration of T cells to the large intestine is dependent on $\alpha_4\beta_7$ but independent of CCR9[185,186] and retinoic acid[187]. Recent work has identified a key role for transforming growth factor-β, combined with unknown factors, in induction of GPR15 expression to drive Treg cell homing to the large but not small intestine[188]. Furthermore, CD4 T cell recruitment to the large intestine has been shown to be chemokine dependent although the chemokines involved have yet to be identified[93]. The differences in homing to the large and small intestine still needs to be further clarified but research in this area has been hampered by a lot of overlap between the chemokines and their receptors.

Natural killer T (NKT) cells are a subset of T cells expressing the TCR/CD3 complex, NK.1 and Ly-49[189] that are CD1d-restricted T cells that respond to lipid rather than protein antigens. NKT cells have both regulatory and effector functions and play critical roles in the regulation of immune responses in many disease settings including cancer[190]. NKT subsets do differ in frequency between the large and small intestine and have been extensively reviewed by van Dieren *et al*[191]. Higher numbers of NKT cells are found in the large intestine (up to 11% are epithelia-associated and 7% LP associated) compared to the small intestine (2%-6% of epithelia-associated lymphocytes)[191,192].

CONCLUSION

We have reviewed, for the first time, the broad regional diversity of the cells, barrier and immune system of the small and large intestine. From the external environment and the microbiome to the cells of the innate and adaptive immune system the small and large intestine have clear differences that have marked effects on functionality and responses to commensal organisms as well as pathogens. Given the significance of the small and large intestine not only functionally but also in terms of disease it is important to understand how these organs and the cells within them function, and how and why they are different. A greater understanding of the immune system-microbiome interactions in the small and large intestine should reveal answers to important unanswered questions about disease susceptibility and mechanisms of inflammation that are specific to the small or large intestine. Specifically, questions to be addressed include: identifying mechanisms of epithelial crosstalk with the microbiome and whether it is the same in small and large intestine, how the microbiome promotes immune function when access to the LP is limited. What the role of innate cells like eosinophils, ILCs and mast cells are in the regions of the gut in homeostasis and inflammation and how do they differ across the GIT, *e.g.,* is CD22 a functional marker on small intestinal eosinophils? How do colonic and small intestinal macrophage and dendritic cell subsets differ functionally across the GIT in homeostasis and infection. A widening awareness of the differences between the small and large intestine can also influence the development of therapeutics, *e.g.,* in instances where probiotics may be beneficial for the treatment of diseases of the small intestinal but not those of the large intestine. In addition, in Crohn's disease which can affect both the small and large intestine we may want to look at using specialised combination therapy in order to tackle the disease in both sites instead of the use of one drug which may be efficacious in one gut region. Although this review has focused on murine studies, some analogous data has been generated for humans but there is even more which remains unknown, especially in homeostasis, in the human GIT. It is clear that we can no longer make assumptions about similarities in function of our gut cells along the GIT.

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