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The Possible Role of Isolated Lymphoid Follicles in Colonic Mucosal Repair

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Abstract The continuous reformation and rapid repair of the colonic mucosa is essential for avoiding the aggregation of pernicious mutations induced by bacterial, toxic, or mitogenic factors. Gut-associated lymphoid tissue is supposed to play a central role in the organization of the repair mechanisms. In inflammatory conditions, the number, the diameter and the density of isolated lymphoid follicles (ILFs) are increasing. They are involved not just in immune surveillance, but their presence is also indispensable in normal mucosal regeneration of the colon. The relation of ILFs to the components of mucosal renewal such as bone marrow derived stem cells, follicular dendritic cells, subepithelial myofibroblasts or crypt formation has not been directly studied, and data about their putative organizer role are scattered in scientific literature. Whether they act as a regenerative pool containing stem cells in case of mucosal damage, or they are responsible only for the optimal cytokine milieu for the differentiation of immigrating stem cells is a question under debate. Our aim is to review the relation of ILFs to the different elements of colonic mucosal repair.

Keywords Isolated lymphoid follicle · Colon · Mucosal repair · Epithelial stem cell · Myofibroblast · Follicular dendritic cell · Bone marrow · Mesenchymal-epithelial transition

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Introduction

Some steps of colonic epithelial regeneration are known, but the connections among them are not fully understood. The continuous reformation of the epithelial layer is important to avoid the aggregation of pernicious mutations induced by bacterial, toxic, or mitogenic factors. In inflammation, the lack of regenerative factors and the disturbance of the regulation of regenerative mechanisms lead to ulcer development. It has been observed, that in colonic inflammation there is a tight connection between the degree of epithelial damage and the number, the diameter and cellular compounds of subepithelial lymphoid follicles [1]. The more severe epithelial destruction develops, the higher number of isolated lymphoid follicles (ILFs) can be found in adjacent mucosa.

It has been recently reported, that besides inflammation, lymphoid follicles are also present in the carcinomas of the lung [2], the endometrium [3], the liver [4], or the colon [1]. They are supposed to have immune-mediated antitumoral effects, as their elevated number are in positive correlation with a better prognosis and a longer survival [2].

However, the exact role of ILFs in colonic mucosal repair is not yet known. Some data show [5] that the lack of lymphoid follicles results abnormal crypt formation due to pathological wound contraction in case of epithelial

destruction. Whether ILFs act as a regenerative pool containing putative stem cells in case of mucosal damage, or they are responsible only for the optimal cytokine milieu for the differentiation of immigrating stem cells need to be further examined.

In this review, our aim is to summarize the current knowledge about ILFs' role in colonic mucosal regeneration, and we also try to discuss the connection between ILFs and the elements of these regenerative processes, that can be seen on Fig. 1.

The Organization of the Mucosa-Associated Lymphoid Tissue

The innate and adaptive components of the mucosa-associated lymphoid tissue (MALT) which forms the largest lymphoid component in the human body and in which approximately 70% of the body's immune cells are found [6], together with the gut epithelium differentiates between pathogens and commensal bacteria. The components of MALT are sometimes subdivided into the following forms: GALT (gut-associated lymphoid tissue), BALT (bronchus-associated lymphoid tissue), NALT (nose-associated lymphoid tissue), LALT (larynx-associated lymphoid tissue), and CALT (conjunctiva-associated lymphoid tissue in the human eye) [7]. SALT (skin-associated lymphoid tissue) [8]

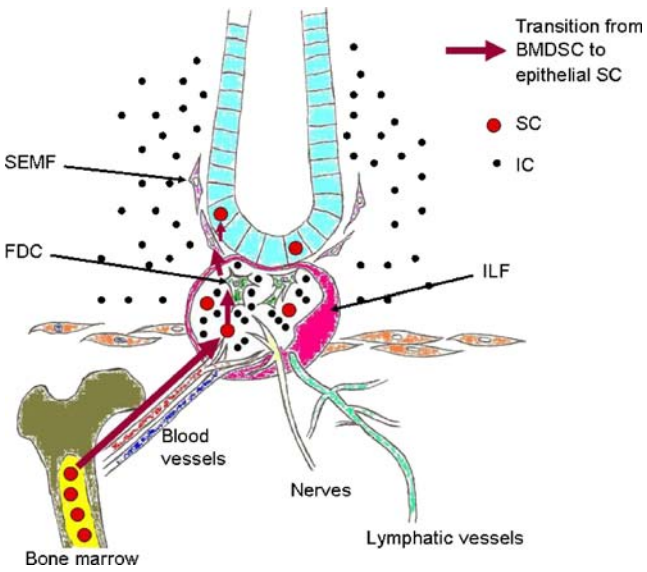

Fig. 1 The elements of colonic mucosal regeneration Based on literature data, it seems that isolated lymphoid follicles (ILF) has an organizer role in case of colonic mucosal damage. Bone marrow derived stem cells (BMDSC) immigrate to the submucosal ILF via the vessels, where they are supposed to be involved in the development of follicular dendritic cells (FDC) which could form subepithelial myofibroblasts (SEMF). Whether the transition of mesenchymal originated stem cells (SC) to epithelial SCs locates to the ILFs is not clear yet. (IC: immune cells)

and VALT (vascular-associated lymphoid tissue) [9] are also known.

Majority of the GALT is composed of isolated and aggregated lymphoid follicles dispersed throughout the small and large intestines [10]. These lymphoid follicles, including Peyer's patches (PP) of the small, and ILFs of the large intestine, are composed of a specialised follicle associated epithelium (FAE) which overlies a subepithelial dome containing numerous dendritic cells, macrophages, T and B lymphocytes [10, 11]. The FAE contains special antigen sampling cells (the so-called microfold or membrane /M/ cells) which transport samples of foreign material by active transepithelial vesicular transport from the lumen directly to intraepithelial lymphoid cells and to subepithelial organized lymphoid tissues [10, 12]. M cells have a crucial role in the initiation of mucosal and systemic immune response [13]. ILFs have in general an average diameter of 0.1–0.7 mm and a number of 30,000 in human [14]. After the induction of PPs and ILFs, immune cells distributed throughout the lamina propria and found outside the PPs and ILFs, such as eosinophils, mast cells, dendritic cells, macrophages, neutophils as well as T and B lymphocytes, migrate to the lamina propria [11].

ILFs and PPs are innervated sites of immune surveillance in the gastrointestinal tract. Functionally, mast cell and eosinophil activation caused by an antigenic trigger, affects both the secretory and motor functions of the intestines [15]. These defensive reactions can be modulated by the enteric nervous system [16]. It has been recently recognised that not just regular mucosa without PPs and ILFs, but also the area of PPs are richly innervated [17]. There is a dense neuronal network at the level of supra-follicular dome region, but not within the germinal centers in human ileal PPs [17]. Neuronal alterations, such as nerve-eosinophil associations or increasing neuronal cell adhesion molecule expression in the PP during parasitic infections may have consequences on particular or pathogen uptake [11]. It is also suggested that enteric and symphatetic neurons are involved during the first stage of neuroinvasion of prions, with neurons connecting to them acting as potential carriers of prions to the central nervous system [18].

Vascularization of ILFs

The lymphatic vascularization of ILFs is composed of submucosal vessels that, after surrounding each lymphoid follicle, anastomose in polyhendric meshes and subsequently surround the nearby lymphoid follicle, wrapping it completely [14]. The fluids of the connective interstitial matrix of tunica mucosa drain into the peripheral absorbent lymphatic apparate vessels of the deeper mucosal portion

[14]. Blood vascularization takes origin from arterioles coming from submucosal vessels, that along their way towards the tunica mucosa, together with lymphatic vessels, send thin ramifications to the germinal center of ILFs [14]. These vessels continue in rich venous network in turn draining into the venules of peri-interfollicular area [14].

Revascularization is a key point of colonic mucosal repair. Vasculogenesis may play double role in mucosal organization: on one hand it is necessary for nutrition and metabolic processes, on the other hand the homing of the repopulating bone marrow derived stem cells to the site of tissue damage may happen via blood vessels.

During inflammatory stages, under the action of some cytokines and signalling originated from intercellular adhesion molecules some of the vessels differentiate into high endothelial venules (HEVs) [19, 20]. In case of lymphocytes and neutrophils, it is supposed that they firstly reach the inflammatory sites via a transcellular pathway through the HEVs [21], but an intercellular pathway is also known [22]. Although, there is no evidence of the similar migration of bone marrow derived stem cell to the site of mucosal damage, but it may be hypothesized the same pathways for them.

Based on the result of *Witmer et al.*, it is also suggested that in lymphoid tissues inculding GALT, the signalling system of the vascular endothelial growth factor and its receptor plays a permanent role in ILFs vasculogenesis [23].

Bone Marrow Derived Stem Cells Immigrating into ILFs

Based on the former results [24–26], emerging evidence suggests that bone marrow derived stem cells contribute to tissue regeneration partly by promoting neovascularization or arteriogenesis. After human hematopoietic cell transplantation epithelial tissue chimerism appears [27, 28]. If female patients had received transplants from male donors, XY-positive epithelial cells can be found in gut epithelium.

The bone marrow origin of epithelial cells may be supposed by such observations in which epithelial cell marker and leukocyte marker double positive cells were found in inflamed mucosa adjacent lymphoid aggregates [29–31]. The presence of cytokeratin, epithelial growth factor receptor or hepatocyte-derived growth factor receptor co-expression in CD45+ cells of ILFs, and our observation that cells positive for CDX2, an epithelial stem cell marker, can be found in the lamina propria of inflamed colon (Fig. 2), may support the mesenchymal origin of epithelial stem cells. Based on these results it seems that ILFs are involved in homing and differentiation of bone marrow derived stem cells in case of colonic mucosal demage.

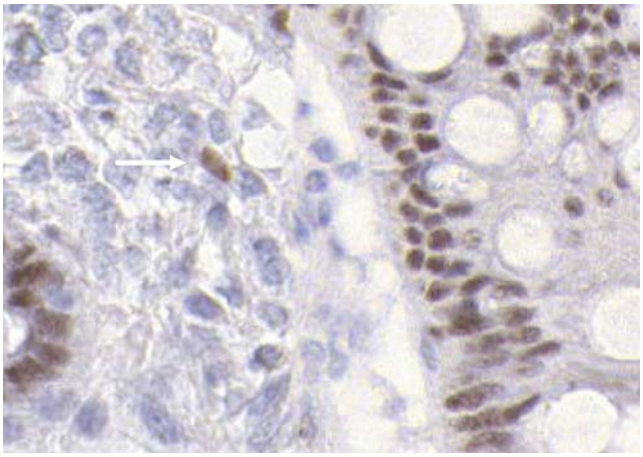

Fig. 2 CDX2 positive cell (*white arrow*) in the subepithelial layer, near to a colonic crypt

Follicular Dendritic Cells in ILFs

Follicular dendritic cells (FDCs) are located in lymphoid follicles within the microenvironment of germinal centers [32, 33]. These cells retain native antigens in the form of immune complexes on their membrane for months, and present these antigens to B cells during the secondary response. FDCs rescue bound B cells from apoptosis, and induce the differentiation of B cells into long-term memory B cell clones [34]. The origin and cell lineage of FDCs are controversial. Whereas their immune functions and expression of antigens associated with hemopoietic cells suggest that they belong to the hemopoietic lineage [35], their spindle-shaped morphology "in vitro," lack of CD45, and presence on FDCs of antigens expressed by fibroblasts [36] indicate that FDCs may be mesenchymal (nonhemopoietic) cells. Based on studies with mouse radiation chimeras, *Humphrey et al.* [37] concluded that FDCs were not derived from the bone marrow, but came from a local mesenchymal precursor. However, *Kapasi et al.* [35], using mice homozygous for the SCID mutation, which lack T, B lymphocytes, and FDCs, demonstrated that after reconstitution with bone marrow from donor mice, the FDCs of the reconstituted mice expressed the donor phenotype. These authors concluded that FDC precursors came from bone marrow.

The low proportion of FDCs in the lymphoid follicle, together with technical difficulties in their isolation, make these cells difficult to study. Based on the results of *Muñoz-Fernández et al.* [38], FDCs seem to be a specialized form of myofibroblasts and derive from bone marrow stromal cell progenitors. These authors were able to isolate and culture 18 follicular dendritic cell lines from human tonsils, which proliferated for as long as 18 weeks and showed a stable antigen phenotype as detected by flow cytometry and RT-PCR. These FDC lines were CD45-negative and

expressed antigens associated to FDCs (CD21, CD23, CD35, CD40, CD73, BAFF, ICAM-1, and VCAM-1) and antigens specific for FDC (DRC-1, CNA.42, and HJ2). These cell lines were also able to bind B cells and secrete CXCL13, and they have functional activities characteristic of FDCs. Nevertheless, the additional expression of STRO-1, together with CD10, CD13, CD29, CD34, CD63, CD73, CD90, ICAM-1, VCAM-1, HLA-DR, alkaline phosphatase, and α-smooth muscle actin (α-SMA) indicated that FDCs are closely related to bone marrow stromal cell progenitors. The expression of α-SMA also relates FDCs with myofibroblasts. Like myofibroblasts, FDC lines expressed stress fibers containing α-SMA and were able to contract collagen gels under the effect of TGFβ1 and platelet-derived growth factor.

Based on their dual phenotype, follicular dendritic cells may represent a transformation switch point among immigrating bone marrow derived stem cells in ILFs and the surrounding subepithelial myofibroblasts.

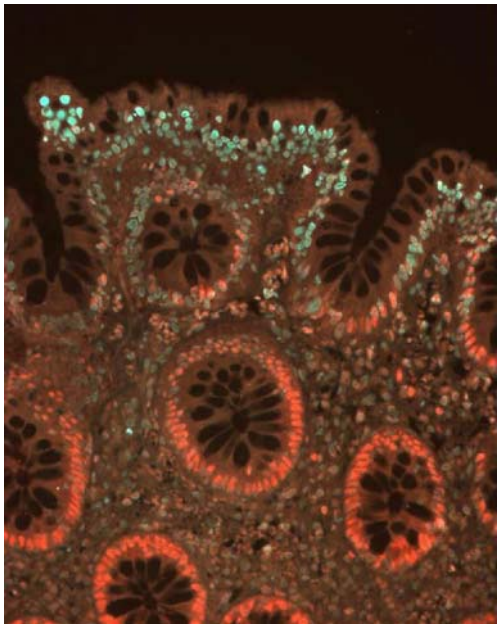

Fig. 3 Parallel labelling of the proliferating (red nuclei) and apoptotic (green nuclei) cells in human colon mucosa (proliferation detection: anti-proliferatin cell nuclear antigen antibody, strepavidin-biotin-Texas Red; apoptosis detection: TUNEL method, FITC)

Subepithelial Myofibroblasts Sorrounding ILF Adjacent Epithelium

Subepithelial myofibroblasts exist as a syncytium that extends throughout the lamina propria of the gut, merging with the pericytes surrounding the blood vessels [39, 40]. SEMFs are invoved in two repair processes of the epithelium [41, 42]. One is called restitution [43]. This is an important response to minor to moderate injury. The second process is observed when the wound is deep, and the subepithelial tissues and the basement membrane need to be reconstituted [42].

According to recent studies [41, 44, 45], myofibroblasts are thought to derive from two major sources, bone marrow, or locally activated fibroblasts, in response to transforming growth factor-β1. In inflammatory circumstances, not just the number of lymphoid aggregates, but the number of bone marrow derived SEMFs are also increased in colonic pericryptal zone [41].

It was recently reported, that in the regenerative phase a significant number of myofibroblasts are present in the deep layer of ulceration of the gastrointestinal tract, showing strong positivity for α-SMA and cytokeratin [46, 47]. These direct evidences supports the hypothesis of SEMFs-to-epithelial cell transition.

Stem Cells in ILF Adjacent Colonic Epithelium

The gastrointestinal epithelium is unique in that cell proliferation, differentiation and apoptosis occur in an orderly fashion along the crypt-villus axis (Fig. 3). The intestinal crypt is mainly a proliferative compartment with monoclonal stem cells, the so-called basal crypt stem cells. Little is known about the phenotype of these cells, although expression of musashi-1 (MSI-1), HES-1 (hairy and enhancer of split homolog-1) and CDX2 has been proposed [48].

In the small intestinal crypts, two stem cell populations are supposed to be; the crypt base columnar cells (CBCs) located amongst Paneth cells, and the label-retaining cells (LRCs) slightly higher up the crypt [49]. In colon only basal crypt stem cells are known. Wnt signalling (among others) from intestinal subepithelial myofibroblasts (SEMFs) helps to regulate crypt stem cell homeostasis. Wnts secreted by SEMFs regulate stem cell self-renewal. Although the presence of stem cells in the proliferative zone of crypts seems to be evident, the way they immigrate the epithelial layer is still remain unknown, and their connection to ILFs is not better than theoretical yet.

Changing Role of ILFs from Immune Surveillance to Colonic Epithelial Renewal?

Beside immune functions, PPs and ILFs are supposed to be involved in mucosal repair via Toll-like receptors (TLRs). In ILFs, TLRs are expressed on the cells of monocyte/macrophage system, some kind of T cells as well as on intestinal epithelial, endothelial- and stromal cells [50]. Using the dextran sodium sulfate (DSS) model of colitis, mice lacking TLR2, TLR4 or MyD88 all developed more

severe colitis than did wild type mice when exposed to orally administered DSS [51]. The more severe colitis in these mice was associated with diminished colonic epithelial proliferation. Administration of broad spectrum antibiotics to wild type mice resulted in the same increase in the severity of DSS colitis as was seen in the knock out mice. These findings suggested that signaling from commensal bacteria throughout TLRs resulted in protection from DSS colitis through enhanced epithelal cell proliferation, and worked as a compensatory factor against epithelial damage [51].

TLRs can bind not only microbial ligands but also endogenous ligands including necrotic cells, heat shock proteins, and components of the extracellular matrix [52–54]. Necrotic cells may activate NFkB through TLR2 leading to the expression of tissue repair-associated genes [52]. It is supposed that necrosis induced inflammation in tissue damage may provide danger signals functioning as inducers of tissue repair responses through TLRs. The TLR ligands released from necrotic cells have not been identified, although heat shock proteins produced by damaged cells are known to be TLR ligands [53]. Components of the extracellular matrix, such as hyaluronan, can be an endogenous ligand for TLR4 [54]. Increased hyaluronan production has been demonstrated in both DSS colitis in mice and in human Crohn's disease [55]. It is possible that TLR activation may occur in the absence of microbial products [55]. In case of inflammatory mucosal damage, ILFs may induce repair mechanisms via endogenous TLR activation.

The Effect of the Presence of ILFs to Mucosal Repair

Intestinal lymphoid tissue has a complex interrelationship with the epithelium. The epithelia of intestinal crypts associated with ILFs and Peyer's patches (PPs) has an increased proliferation rate [5]. *Saxena et al.* showed in rats that without PPs the early phase of mucosal regeneration, both epithelial cell proliferation and migration were decreased, as well as crypt cell production rate in the lesion-adjacent normal mucosa. The lack of the PPs resulted in less well-developed crypts and villi. Wound contraction, however, was greater in the intestinal defect adjacent to the PP. They concluded that PPs have a facilitative effect on the healing of intestinal wounds by promoting both epithelial cell migration on the defect and epithelial cell proliferation in the crypts adjacent to the wound and by decreasing the rate of wound contraction. Their findings support the role for intestinal lymphoid tissue in the regulation of epithelial cell maintenance.

In rats, a difference of epithelial apoptosis between the FAE of PPs and intestinal villi was described [56]. Observing cleaved caspase-9 and -3, DNase I-, and Bcl-x expression and nuclear DNA fragmentation, *Onishi S et al.* showed that the progression of the apoptotic process in the epithelial cells of FAE is later than in the intestinal villi, so that the possibility of epithelial differentiation might be remained in the FAE, unlike in the intestinal villi. PPs are supposed to have a regulatory effect on the epithelial proliferation as well [57]. *Renes et al*. assayed methotrexate (MTX)-induced epithelial damage in rats. The main alterations between PP and non-PP epithelium after MTX treatment were found in PP crypt epithelial proliferation, on both mRNA and protein levels.

The Wnt signaling pathway is critical for regulating a number of basic cell functions, such as cell proliferation, cell fate, polarity, differentiation, and migration, leading to morphogenesis and organogenesis [58, 59]. There is strong genetic evidence that Wnt signaling plays critical roles in the regulation of epithelial stem cells in the intestinal tract [60]. The Wnt target gene Lgr5 has been recently identified as a novel stem cell marker of the intestinal epithelium and the hair follicle [61]. In the intestine, Lrg5 is exclusively expressed in cycling crypt base columnar cells [61]. Many Wnt family proteins are expressed in hematopoietic tissues, and also can be secreted by lymphoid cells [62, 63]. The Wnt-Lrg5 pathway may be a potential switch between the ILFs and colonic epithelial renewal. Lymphoid cells of ILFs may produce Wnts which are essential components of a milieu in which bone marrow derived stem cells immigrated to ILFs turn into epithelial differentiation. This hypothesis may help to understand such still unpublished observations that colonic crypts "outgrow" from ILFs (Fig. 4).

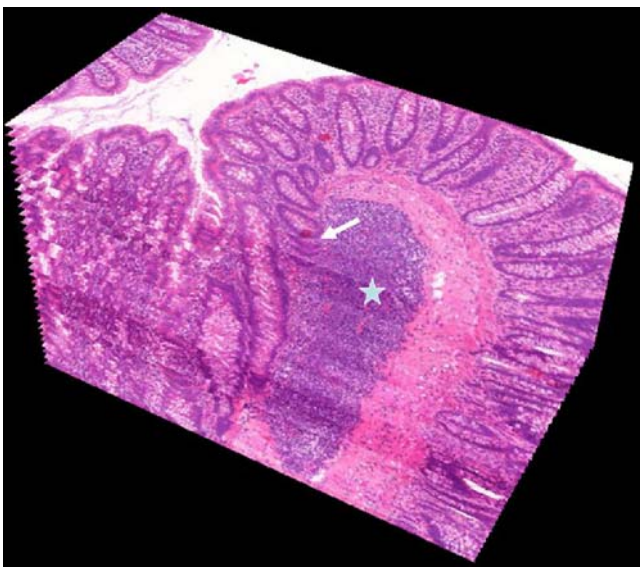

Fig. 4 3D reconstruction of a surgical sample from the human colon (MIRAX Viewer, 3D, 3DHISTECH Ltd., Budapest). An isolated lymphoid follicle (*white star*) can be seen in the submucosa. Colonic crypts (*white arrow*) with no connection to the luminal surface almost "outgrow" from the ILF

Mesenchymal-Epithelial Transition in ILFs?

The epithelial-to-mesencyhmal (EMT) transition is a physiological mechanism present during development, and is also encountered in several pathological situations such as renal interstitial fibrosis, endometrial adhesion, or cancer metastasis [64]. A reverse phenomenon, the mesencyhmal-to-epitehelial transition (MET) also takes place during normal development, in processes like somitogenesis, kidney development, coelomic cavity formation [65]. In adult organisms, it has been proposed that restrictive mechanisms repress EMT and MET [66]. During tumour development, these mechanisms appear to fail, allowing EMT described in metastasis generation [67].

In inflammation, EMT and MET can also be altered, because mesenchymal stem cells are mobilized to these sites of injury and consequently subjected to the inflammatory response [68]. Although there are no data about a potential MET beyong these circumstances, it was published that bone marrow derived stem cells could differentiate into mature-appearing epithelial cells in response to tissue damage [69].

There are several possible mechanisms by which bone marrow derived stem cells become nonhematopoietic cell types, such as epithelial cells [70]. One mechanism could be that there is a population of highly pluripotent stem cells located in the bone marrow that have not yet committed to hematopoiesis. Alternatively, committed hematopoietic stem cells can transdifferentiate, that is, change their gene expression pattern from that of one cell type to that of a completely disparate cell type. Another alternative mechanism could be the fusion of a bone marrow derived cell, such as a macrophage, with a nonhematopoietic cell to form a heterokaryon, in which case the gene expression pattern of the macrophage is reprogrammed by transcription factors or other cytoplasmic mediators to be more like that of the non-hematopoietic fusion partner. This has been shown to occur by *in vitro* fusion of fibroblasts with myoblasts, which results in expression of muscle-specific mRNA by the fibroblast nucleus [71].

It was recently published, that versican, a large chondroitin sulfate proteoglycan mediates MET [72]. The results of *Hirose J et al.* [73] indicate that versican can bind specific chemokines through its chondroitin sulfate chains and that the binding tends to down-regulate the chemokine function. This raises the possibility that versican may act as a regenerative factor in colonic mucosa, and may be an important switch point between ILFs and MET. Our unpublished data, in which CDX2 positive cells were mainly found in the marginal zone of ILFs is also suggests that MET may takes place in these immune formations.

Conclusions

Based on the summarized results of literature, it seems that ILFs are expressly involved in the mucosal regeneration of the colon. Subepithelial revascularization after mucosal damage partly takes place under the direction of ILFs with the prominent help of vascular endothelial growth factor and its receptors. Immigrating stem cells from bone marrow may leave circulation via high endotehlial venules in ILFs and their surroundings. Their differentiation throughout mesencymal-to-epithelial transition also may happen in ILFs, and follicular dendritic cells as well as the subepithelial myofibroblasts seem to be crucial parts of colonic crypt formation and epithelial renewal.

The better understanding of ILFs' role in mucosal repair may lead to the development of such new therapeutic agents for inflammatory colon diseases that not just decrease the activity of inflammation, but accelerate epithelial barrier recovery, hence dramatically decrease clinical symptoms.

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