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ORIGINAL ARTICLE

Epithelial Cells Orchestrate the Functions of Dendritic Cells in Intestinal Homeostasis

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ABSTRACT

The gastrointestinal tract represents the largest mucosal membrane surface and is the one of the most complex human organs. The intestinal barrier dysfunction contributes to systemic immune activation. The mucosal immune system has extremely arduous tasks to resist invaders and promote tolerance of food antigens and the microbiota. The intestinal mucosal immune system fulfills these tasks through complex interactions between immune cells and the local microenvironment in intestine. Intestinal Epithelial Cells (IECs) play important roles in these complex interactions. IECs not only constitute the first barrier of the intestine but also are crucial for integrating external and internal signals and for coordinating the ensuing immune response. Dendritic Cells (DCs) play key roles in shaping the intestinal immune response by their ability to coordinate protective immunity and immune tolerance in the host. DCs are pivotal actors in the connection between innate and adaptive immune responses. The IECs coordinate with the DCs in immune recognition, tolerance and host defense mechanisms. In this review, we will summarize how IECs orchestrate intestinal DCs in intestinal homeostasis and diseases.

INTRODUCTION

IECs play a significantly role in the continuous maintenance of intestinal homeostasis. Through the secretion and the maintenance of a continuous cell layer, IECs effectively maintains a physical and biochemical barrier between the hosts and their environment. As IECs form a uniquely adapted barrier surface, they actively respond to their local environment through regulatory mechanisms that make IECs recognition as central mediators of microbial and immune homeostasis in the intestine. IECs not only constitute the first line defense of intestinal [1] but also constantly pass signal information between the gut lumen and immune cells. DCs are the guard of immune cells. They play a central role in the maintenance of intestinal homeostasis and the initiation of adaptive immune responses. DCs are professional Antigen Presenting Cells (APCs) that coordinate innate and adaptive immune responses. In addition to antigen presentation, mucosal DCs are mainly also participate in IgA type switching. $CD103^+$DCs interact with IECs in the intestinal barrier, promoting the Forkhead Box $P3^+$ ($Foxp3^+$) to regulate the differentiation of T cells through Transforming Growth Factor-β (TGF-β) and Retinoic Acid (RA)-dependent mechanisms, thereby promoting immune tolerance. In addition, IECs regulate $CD103^+$DCs to form intestinal homing properties to T cells. Therefore, in addition to promoting the maturation of naive T cells based on antigen-specificity, $CD103^+$DCs can also play a role in fundraising at the initiation site of epithelial

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barrier antigens. So IECs actively influence the activating properties of bystander DCs, which helps to regulate immune homeostasis.

INTESTINAL EPITHELIAL BARRIER SYSTEM

Cellular components

The intestinal epithelium has absorption, secretion and digestion functions. It consists of a monolayer of simple columnar epithelial cells and is folded to create crypt and villus structures. It includes differentiated cells of various lineages-absorptive intestinal cells, goblet cells, enteroendocrine cells, Paneth cells, tufted cells and microfold cells (M cells)-all of which are derived from intestinal stem cells [2]. In the small intestine the vast majority of villous cells are absorptive enterocytes which are responsible for nutrient absorption [3]. Goblet cells produce mucus that prevents intestinal bacterial directly adhesion to the intestinal epithelium, thereby spatially modulating the colonization of commensal bacteria [4]. In the process of intestinal mucosal protection, goblet cells secrete highly glycosylated mucin into the intestinal lumen, creating a first line of defense against microbial invasion. The most abundant Mucin 2 (MUC2) of these mucins plays an important role in the organization of the intestinal mucous layers at the epithelial surface of the colon [5]. In addition, goblet cells also Secrete Trefoil Factors (TFFs) (primarily TFF3) and resistin-like molecule-β (RELM-β). MUC2 and RELM-β regulate the physical barrier, microbial defense and injury repair responses in the intestine [6,7]. Beyond mucus production, goblet cells present antigens which acquired from the intestinal lumen to DCs of the Lamina Propria (LP) and play a key role in the modulation of the intestinal microbiome, too [8]. Paneth cells residing at the base of small intestinal crypts produce and secrete antimicrobial proteins to limit bacterial invasion [9]. α-defensins which is the major antimicrobial peptides in small intestine is secreted only by Paneth cells in intestinal epithelium. Paneth cells secrected α-defensins immediately in response to microbe stimuli, revealing their important role in mucosal immunity [10]. Tuft cells constitute a minor fraction (0.4%) of the intestinal epithelium [11]. They elicit an immune response, especially against intestinal parasitic infections [2]. Enteroendocrine cells occupy approximately 1% of IECs and secret more than 20 peptide hormones. Beyond luminal nutrients sensing and absorption, enteroendocrine cells act as important mediators of intestinal infection and play immunomodulatory roles in mucosal immunity [12]. Approximately 10% of the IECs that cover the organized lymphoid follicles of the Gut-Associated Lymphoid Tissues (GALT) are M cells. M cells are specifically used to take in intestinal luminal antigens to regulate mucosal immune responses [2].

The mucus coat

The mucins and lipids of the intestinal mucosal surface safeguard IECs from a variety of sheer forces and physical trauma within the lumen, and prevent direct contact of the intestinal epithelium with microorganisms [13]. Mucus is consisted of all kinds of large and complex molecules, and mucin is the most representative. In small and large intestine, MUC2 which is synthesized and secreted by goblet cells is the most common mucin. There are reports that MUC2-deficient mice have no a mucus layer, making IECs contact directly with commensal bacteria, which leads to spontaneous colitis and colorectal cancer [14,15]. TFF3 is another important component of mucus. TFF3 which is secreted also by goblet cells is a small peptide and may resistant protease [16]. In addition to these physical functions, antimicrobial molecules are secreted to isolate bacterial further in the mucus coat. These molecules include the substances derived from IECs such as Antimicrobial Peptides (AMPs) and the substances derived from non-IECs such as Secretory Iga (SIgA), which is transcytosed by the IECs [17]. The secreted mucins are a well-known source of nutrients for the bacterial species composing the intestinal microbiota [18].

Pattern-recognition receptors are sensors of the epithelial barrier

IECs express Pattern-Recognition Receptors (PRRs) that act as dynamic sensors for the microbial environment and as active participants in the regulation of mucosal immune cell responses [5]. These PRRs are segmented into three families: Toll-Like Receptors (TLRs), Retinoic Acid Inducible Gene I (RIG-I)-like receptors (RLRs) and Nucleotide Oligomerization Domain (NOD)-like receptors (NLRs) [19]. The TLR family is primely studied, and 13 TLRs have been reported in mice and humans [19]. TLR signalings in the intestine are involved in epithelial cell proliferation, IgA production, tight junction maintenance and antimicrobial peptide expression, which play important roles in maintaining a healthy epithelial barrier [20]. The recognition of Pathogen-Associated Molecular Patterns (PAMPs) by TLRs can activate many signaling pathways. Such as the Myeloid Differentiation Primary-Response Protein 88 (MyD88)-dependent TLR pathways can activate the Nuclear Factor-Kappa B (NF-κB) and the Activate Protein-1(AP-1) signaling pathways, but the Toll/IL-1R Domain-Containing Adaptor-Inducing IFN-β (TRIF)-dependent TLR pathways can activate the Type I Interferons (IFNs) signaling pathways [21]. RLRs are viral RNA sensors located in cytosol. The RLR family is consisted of RIG-I, Melanoma Differentiation-Associated Protein 5(MDA5), the Laboratory of Genetics and Physiology Protein 2 (LGP2) [22]. RIG-I and MDA5 contain N-terminal tandem Caspase Activation and Recruitment Domains (CARDs) but LGP2 lacks CARDs function only as a regulator of RIG-I and MDA5 [23]. RIG-I and MDA5 recognize distinct viral RNA species binding to their

common adaptor Mitochondrial Antiviral Signaling (MAVS) through CARD–CARD interactions and ultimately activate transcription of IFNs and proinflammatory cytokines [24-25]. The NLRs are also innate immune receptors modulating the immune response of intestinal immune barrier. Unlike TLRs, NLRs are identified cytoplasmic PRR for the presence of intracellular pathogens [26]. NOD1 and NOD2 are two prototypic NLRs and activate NF-κB and mitogen activated protein kinase ((MAPK) inflammatory signaling cascades in a manner similar to TLR [21]. NLRs are not only activate NF-κB and MAPK pathways, but also they are known to form inflammasome, which is a multimeric protein complex that activates caspase-1 and induces the processing and maturation of proinflammatory cytokines Interleukin (IL)-1β and IL-18 [27]. NLRs play important roles in defending against pathogens. And their abnormalities will lead to various intestinal diseases. NOD1 recognises only Gram negative [28], whereas NOD2 recognises both Gram positive and Gram negative bacteria by recognizing Muramyl Dipeptide (MDP) [29]. There is a report that double $NOD1^{-/-}$/$NOD2^{-/-}$ mice have an heightened susceptibility to colitis due to increased paracellular permeability, decreased E-cadherin, and lowed colonic antimicrobial Regenerative III protein (RegIII-γ) [30]. NOD2 mutations are associated with an enhanced risk of Crohn's disease [31] and colorectal cancer [32].

INTESTINAL DCS

Intestinal DCs are distinct from macrophages

DCs are located mainly in the LP and the GALT of the small and large intestine, which includes isolated lymphoid follicles, Peyer's Patches (PPs) and the Mesenteric Lymph Nodes (MLNs) [33]. DCs are Bone Marrow (BM)-derived antigen presenting cells that comprise two major subgroups: Conventional (or classical) DC (cDC) and plasmacytoid DC (pDC). They are different in development from both tissue resident Macrophages (Mfs) and monocyte-derived populations [34]. Because DCs and Mfs are the coexpression of CD11c and class II Major Histocompatibility Complex (MHCII) in the gut [35]. This requires that the identification of intestinal Mfs and DCs must detect many surface markers in combination and analyse multi-parameter. Some studies have showed that DCs express CD103 (integrin aE), but Mfs don't express CD103 and express highly chemokine CX_3C receptor 1(CX_3CR1), pan-Mf marker F4/80, Mf-specific high affinity FcgRI and CD64 [35-38]. So the flow cytometry and histology in mice harboring a Green Fluorescent Protein (GFP) reporter gene insertion in their CX_3CR1 gene, in combination with CD11c and MHCII are used to distinguish Mfs from DCs [39]. There is now consensus that in fact intestinal CX_3CR1^{hi} Mfs expressing F4/80, CD11b, and CD64 are Mfs [36,37]. CX_3CR1^{hi} Mfs possess high phagocytic activity and classical Mfs morphology, including cytoplasmic vacuoles and abundant cytoplasm [36]. $CD64^{-}$ $F4/80^{-}CD103^{+}CD11c^{+}MHCII^{+}$Mfs possess characteristics of bona fide DCs, including the ability to prime naı¨ve T cells efficiently, to induce the expression of gut homing markers on T cells, and the differentiation of $Foxp3^{+}$ Regulatory T (Treg) cells. It is important to mention that the intestinal DC compartment is itself heterogeneous, on the basis of the expression of CD103 and CD11b to identify DC subsets. Although for a long time it was consensus that all mucosal DCs expressed CD103, now it is found out that bona fide $CD103^{-}$ DCs are existence [38-40] and CD103 cannot act as the facto marker of mucosal DCs. Because $CD103^{-}CD11b^{+}$DCs also express CX_3CR1, making them fall under Mfs [41,42].

Intestinal DC ontogeny

Intestinal DCs differentiate from specialized DC lineage-committed BM progenitors. Commitment to the mononuclear phagocyte lineage was Mfs and MDP, a dedicated BM precursor that has lost granulocytic, erythrocytic and megakaryocytic potential [43]. MDP may differentiate into either monocytes which germinate most tissue Mfs or into a DC-restricted progenitor called the Common Dc Precursor (CDP) which germinate both classical or plasmacytoid DCs [44]. The CDPs and pre-DCs in the intestine germinate only $CD103^{+}CD11b$ and $CD103^{+}CD11b^{+}$ but not germinate $CD103^{-}$ $CD11b^{+}$DCs. But monocytes may differentiate into $CD103^{-}$ $CD11b^{+}$ [45]. These clearly show that intestinal $CD103^{+}$ and $CD103^{-}$ DCs derive from two independent lineages. And $CD103^{-}CD11b^{+}$DCs origining from the monocyte may indeed represent intestinal Mfs [46].

A large amount of growth factors take part in the maturation of the Mfs and DCs. The development of intestinal Mfs requires the Colony-Stimulating Factor 1(Csf-1; previously named Macrophage Colony-Stimulating Factor, M-CSF). The development of DCs needs Fms-Like Thyrosine Kinase 3 (Flt3) ligand (Flt3L) and Colony-Stimulating Factor 2(Csf-2; previously named Granulocyte Macrophage Colony-Stimulating Factor, (GM-CSF) [42]. Flt3 and Flt3L are responsible for the differentiation of $CD103^{+}$ $CD11b^{-}$ and $CD103^{+}CD11b^{+}$DCs, and GM-CSF controls the differentiation of $CD103^{+}CD11b^{+}$DCs [45-47].

Recently it has found that transcription factors participate in the development and maintenance of intestinal DCs, too. Basic Leucine Zipper Protein ATF-Like 3(BATF3), Interferon Regulatory Factors (IRF) 8 and Inhibitor of DNA Binding (Id)-2 have been shown to control intestinal $CD103^{+}CD11b^{-}$ DCs development while IRF4 and Notch2 have been shown to control $CD103^{+}CD11b^{+}$DCs development [48-52]. But the above transcription factors cut no ice in development of $CD103^{+}CD11b^{+}$DCs [46].

Antigen acquision and presentation to T cells

Which DCs uptake foreign antigen to T cells are essential for stimulating antigen-specific immunity or the induction of oral tolerance. DCs closely interact with the intestinal epithelium through projecting dendrite penetrating

epithelial layers to extend into the lumen to capture luminal bacteria. Intestinal CX_3CR1^{hi} Mfs form Transepithelial Dendritics (TEDs). Thus CX_3CR1^{hi} Mfs may capture particulate antigen from the intestinal lumen [53]. There are report that $CD103^+$ DCs extend them dendrite penetrating epithelial layers to capture antigen and potentially acquire also luminal Salmonella. In this progress goblet cells which potentially acquire also luminal Salmonella play a pipe role to submit luminal antigens to LP DCs [8,54,55].

The DCs migrating to the afferent lymphatics submit mature antigens to T cells in the form of peptide–MHC complexes in tissues [56]. $CD103^+$ DCs found in the MLNs were reported to be migratory cells from tissues: after mice injected with 5-Bromo-2'-Deoxyuridine (BrdU), labeled $CD103^+$ DCs delayed emerging in MLNs compared with the LP [57]. CX_3CR1^+ LP Mfs were non-migratory cells because CX_3CR1^+ Mfs were not detected in the MLNs and did not contribute to the cell-associated spread of *Salmonella* from the intestine to the MLNs [45]. Under homeostatic conditions, DCs continue to patrol the LP. Upon antigen encounter, DC initiates C-C motif Chemokine Receptor 7 (CCR7) expression and migrates into lymph nodes to direct T cell activation and differentiation [34]. Consistently, CCR7 is present on maturing CX_3CR1^- DCs, but not on CX_3CR1^+ Mfs in the LP [58]. Indeed, $CD103^+$ DCs deregulate CCR7 before migrating to MLNs, but CCR7-deficient DCs faile to transfer [59]. These results show that $CD103^+$ DCs are the primary DCs which presents oral antigens to T cells of MLN in the steady state. The oral or intra-peritoneal adjuvants (including TLR agonists) administration can significantly reinforce the migration of DCs from the intestinal LP to draining MLNs [60]. The immigrating $CD103^+$ LP DCs in the MLNs induce $FoxP3^+$ Treg cells development and make the feature of gut homing molecules on T and B cells [61]. However, the exact mechanisms which the DCs of LP present intestinal antigens to the MLNs is still a hot spot of investigation.

IECS ORCHESTRATE DCS IN STEADY STATE

Induction of tolerogenic DCs

Human IECs play an important role in driving the development of non-inflammatory DCs [62]. IECs and DCs constantly "crosstalk" with each other. And this crosstalk can help gut to maintain immune homeostasis *via* inducing non-inflammatory DCs. Some results indicate that IECs can "educate" tolerogenic DCs, thus inducing Treg cell differentiation [63,64]. This process is mediated by the combination of Thymic Stromal Lymphopoietin (TSLP), RA, TGF-β and the different cytokines that are constitutively expressed during the crosstalk [65-70] (Figure 1). TSLP inhibits IL-12 production of DCs in response to bacteria and drives the development of Th2-polarizing DCs. TGF-β and RA are responsible for driving the development of $CD103^+$ tolerogenic DCs in $CD103^-$ cells. These cells also inhibit the development of Th1 and Th17 cells, suggesting that IECs imprints a complete mucosal phenotype on DCs [62]. Both human and mouse IECs secrete TGF-β to promote the development of tolerogenic DCs which express $CD103^+$ [71]. As mentioned above, $CD103^+$ DCs can induce the differentiation of Treg cells [65-71]. As a regulatory cytokine, TGF–β plays a key role in gut APCs. TGF-β plays an important part in promoting and generating $Foxp3^+$ Treg cells in the intestinal compartment [63-70]. And TGF-β may inhibit Mfs and DCs to express proinflammatory cytokines [72]. When cocultured with IECs, DCs acquired an ability to produce TGF-β, while neutralized with anti-TGF-β antibodies, the ability of DCs inducing Treg cell differentiation was reduced significantly [64]. RA is the active metabolite of vitamin A and modulates intestinal immunity. The cells that express Retinal Aldehyde Dehydrogenases (RALDHs) generate RA. RA acts on Retinoic Acid Receptor (RAR) in various cells. Many factors such as vitamin A, fatty acids, the TLR ligands, GM-CSF and IL-4 influence RA generation and promote RA synthesis [73]; while prostaglandin E2 inhibits RA synthesis [74]. IEC-derived RA also participates in the induction of tolerogenic DCs. Due to the metabolism of vitamin A from dietary in IECs, RA is abound in the small intestine. DCs can respond directly to RA because DCs express RAR, particularly RAR-α [75]. So intestinal DCs present antigens to T cells along with RA [76]. And RA is also able to enhance TGF-β -induced Foxp3 expression in T cells [77]. TSLP which expresses on IECs is another potent activator of DCs [66]. The IL-7 Receptor A-Chain (IL-7Rα) and TSLP Receptor (TSLPR) are two primary TSLPRs [78]. EC-derived TSLP also plays an important part in the induction of tolerogenic DCs by inducing the expression of CD103 on DCs [71]. One study showed that TGF-β, Aldehyde Dehydrogenase-1A1 (ALDH1A1) and TSLP might intercoordination during the development of Treg cells [72]. Another study showed that IECs regulated the function of DCs through secreting integrin αvβ6 [79]. Moreover, MUC2 induced additional DC-conditioning signals through IECs and promoted their tolerogenic properties [80].

Induction of T cell immunity

As mentioned above, DC-IECs interact with each other through TSLP, RA, TGF-β and other cytokines. These factors also determine T cell differentiation, functional properties, polarizing signals and types of T cell (namely, Th1, Th2, Th17, or Treg cell) responses [68] as well as gut homing properties. So TSLP, RA and TGF-β play major roles in the crosstalk of intestinal DC-IECs. As we mentioned above, TGF-β, ALDH1A1 and TSLP promote the development of $CD103^+$ tolerogenic DCs (Figure 1), which are able to make naive $CD4^+$ T cells split up into $CD4^+CD25^+Foxp3^+$ Treg cells [64-81]. EC-conditioned DCs promote Th2 cell responses but simultaneously die away promoting Th1 and Th17 differentiation in response to microbial stimuli [64-82]. The some studies proved that IEC-DCs produced significantly more IL-10 and IL-2, IL-4, IL-5, IL-13 but less IL-12p70

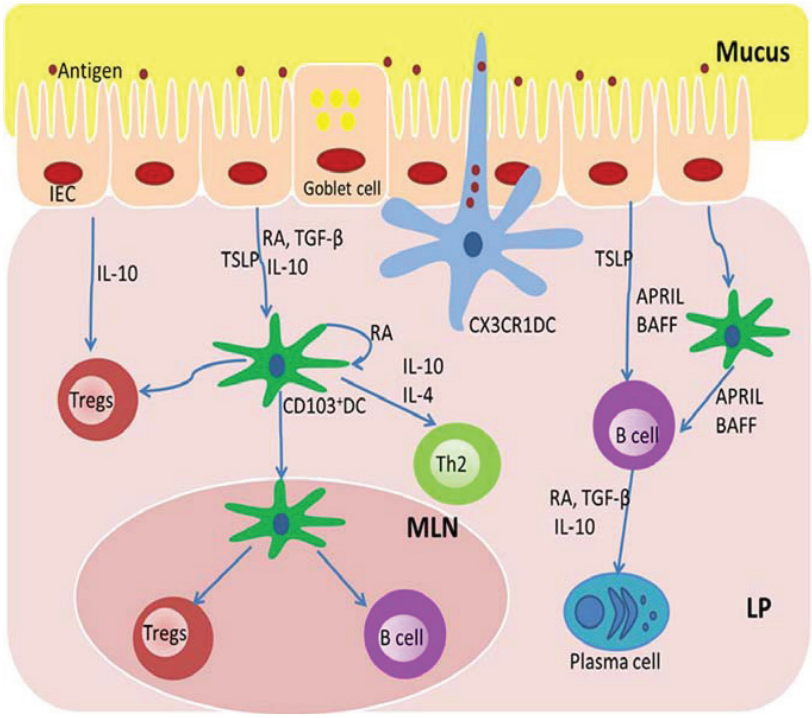

Figure 1 Interaction between intestinal epithelial cells and dendritic cells.

compared with non-conditioned DCs, so IEC-DCs induced classical noninflammatory Th2 responses, while non-conditioned DCs induced Th1 responses [63-66]. TSLP-DCs can promote Th2 cell responses by upregulating OX40-Ligand (OX40L) and producing IL-13, IL-5 and IL-4 [83]. RA promotes the expression of α4β7 and C-C Motif Chemokine Receptor 9 (CCR9) which are the gut-homing molecules on $CD4^+$ T cells. So RA can enhance $CD4^+$ T cells to migrate into the LP and GALT. RA enhances Treg cells differentiation and weaks Th1 and Th17 cells differentiation [68]. RA also sustains the stability and function of Induced Regulatory T (iTreg) cells, even under inflammatory conditions, which further results in tolerance induction [84]. DCs can also release Indoleamine 2, 3-Dioxygenase (IDO) [85]. IDO is a potent activator of $Foxp3^+$ Treg cells, but when IDO is blocked, $Foxp3^+$ Treg cells undergo a IL-6-driven reprogramming into proinflammatory phenotype similar to Th17 cells and produce pro-inflammatory cytokines such as tumor necrosis factor α (TNF-α), IL-17 and IL-22 [83-86].

Induction of B cell immunity

DCs are not only often described as their ability to elicit T cell responses, but also can directly activate B cells. DCs can present unprocessed antigens to B cells and can affect the differentiation and survival of antibody-secreting cells [87]. DCs (especially plasmacytoid) and IECs product cytokines such as the tumor necrosis family members B Cell Activating Factors (BAFF) and A Proliferation-Inducing Ligand (APRIL) to initiate the Class-Switch Recombination (CSR) from IgM to IgA [88].

BAFF and APRIL not only activate IgA production but also sustain the survival of B cells and plasma cells [89]. In this process TSLP is a key factor (Figure 1). By conditioned DCs and IECs, TSLP facilitates the release of BAFF and APRIL and may further amplify their IgA-inducing function [88-90]. In addition, TSLP promotes IgA class switching in the LP, too [90]. IL-10 and TGF-β are also IgA-inducing cytokines that participate in IgA class switching in response to TLR signals from intestinal pathogens [91-92]. Intestinal DCs not only directly active B cell responses, but also they induce B cells to express α4β7 and CCR9 which are gut-homing receptors [93]. The RA of DCs induce tolerogenic $Foxp3^+$ Treg cells so that skews the responses of intestinal B cell toward IgA production [94] (Figure 1). On IgA-expressing B cells, RA possesss IgA-inducing activity through triggering the expression of gut-homing molecules- α4β7 and CCR9 [95]. In addition, RA production is the one of the significance factors which drive the CSR of IgM-positive B cells to IgA [96]. Cooperating with TGF-β, RA promotes both the IgA CSR and the IgA production of B cells [96]. In vitro study, RA also substantially enhanced IgA production cooperating with IL-5 and/or IL-6 and DCs [93]. B cell conversion into Regulatory B Cells (Breg), which produce IL-10 and suppress experimental colitis, is partially dependent on RA production by DCs [94].

Induction of intestinal SIgA

For a long time, SIgA has been recognized as the first line of defense against IECs from intestinal pathogens and toxins [97]. It is able to maintain non-invasive intestinal

bacteria and neutralize invasive pathogens through a variety of mechanisms [98]. SIgA are exclusively present at the mucosal surface and consists of a dimeric IgA linked to a Secretory Component (SC) by a J chain. SC is the extracellular part of Poly Ig Receptor (pIgR) which is synthesized by IECs. SC protects SIgA from degradation by microorganisms and host proteolytic enzymes in the Gastrointestinal (GI) tract and body secretions [99]. To induce intestinal SIgA, both T cell-dependent and T cell-independent modes are proposed. In the T cell-dependent model, M cells and intraepithelial DCs sample and deliver antigens from the intestinal lumen to APCs (like DCs and Mfs) in the underlying subepithelial dome region. Antigen sampling by intestinal M cells is the principal pathway initiating mucosal SIgA production [100]. The interaction between APCs and Th2 lymphocytes leads to the release of Th2 cytokines, including IL-4, IL-5, IL-6, IL10, IL-13 and TGF-β. TGF-β is required for activation and CSR of IgM^+ B cells to IgA^+ B lymphocytes, and IL-4, -5, -6, -10 and -13 promote the proliferation and differentiation of IgA^+ B cells [101]. Final IgA^+ B cells differentiate into plasma cells that secrete IgA [101]. The production of most intestinal IgA in the extrafollicular structure, such as isolated lymphoid follicles and LP, depends on the T cell independent pathway [100]. In T cell-independent responses, the B cells are activated through B-Cell Receptor (BCR) and TLRs recognizing microbial signatures. Other costimulatory signals such as BAFF, APRIL, RA and Nitric Oxide (NO) also promote CSR of IgA. In addition to induce IgA secretion together with IL-5 and IL-6, RA also induces the expression of homing receptors on intestinal B cells [99].

IECS ORCHESTRATE DCS IN INFLAMMATION

Recent evidence has demonstrated that under homeostatic conditions, DCs can detect tolerogenic factors such as RA and TGF-β secreted by IECs through p38 signaling to regulate the expression of TGF-β2, further promoting $Foxp3^+$ iTreg differentiation and T cell homing, thereby maintaining intestinal immune tolerance [102]. During experimental colitis intestinal $CD103^+$DCs migrate to the MLNs and accumulate in the MLNs, where they express lower TGF-β and RALDHs that are required for the generation of RA [102]. TSLP secreted by $CD103^+$DCs and IECs restrains Th17 responses during the steady state and is down-regulated during experimental colitis [67]. Thus, instead of efficiently priming $Foxp3^+$ Treg cells, inflammatory DCs preferentially induce Th1 and Th17 responses during colitis. Flagellin is widely distributed and presents all features of PAMPs [103]. Flagellin can induce IECs to release macrophage inflammatory protein-3(MIP-3α), a chemokine which is responsible for the recruitment of immature DCs. Recently there was the report which in small-intestine LP $CD11b^+$DCs could express TLR5. TLR5 responded to flagellin, which promoted the differentions of Th1 and Th17 cells as well as the differentiation of IgA-producing plasma cells [104]. Flagellin-mediated stimulation of TLR5 on LP $CD103^+CD11b^+$DCs can rapidly and transiently increases the production of IL-23, which, in turn, can induce IL-22 to mediate the expression of the antimicrobial peptide-RegIIIg. In addition, the NF-κb-Inducing Kinase (NIK) signal axis promotes TLR-stimulated IL-23 production, thereby maintaining the abundance of Th17 cells and type 3 innate lymphoid cells (ILC3s), The DC-specific NIK is required for maintaining pIgR expression in IECs and IgA secretion in B cells, as well as involved in modulation of microbiota composition [105]. MUC2 secreted by goblet cells possesss anti-inflammatory abilities, so it also can imprint DCs [80]. Moreover, it was demonstrated that the expression of IL-17 increased significantly in the distal and middle colon and IL-6 and IL-1β which taked part in Th17 development also increased in $Muc2^{-/-}$ mice with extensive colitis [106].

The cell injury signal-extracellular Adenosine-5'-Triphosphate (ATP) enhances also DC activation and immune responses to commensal antigens and switches IECs from tolerogenic to proinflammatory [107]. NOD2 of IECs also plays a key role in educating DCs. During infection by Trichuris murisa, $Nod2^{-/-}$ mice decreased $CD103^+$ DCs to recruit to the epithelium and delayed parasite expulsion kinetics [108]. Besides intestinal pathogens, physiological apoptosis of IECs also plays an important part in regulating intestinal immune responses. Epithelial tissues are characterized with their rapid turnover rate. Intestinal bacteria stimulate $CX_3CR1^+CD103^-CD11b^+$ DCs to produce IFN-β, which promotes the proliferation of Treg cells. But apoptotic epithelial cells regulated negatively the proliferation of Treg cells. This is because the phosphatidylserine of apoptotic epithelial cells suppresses the DCs to produce IFN-β, thus to inhibite Treg cell proliferation [109]. So the crosstalk of IECs and DCs influented significantly the intestinal inflammatory.

IECS ORCHESTRATE DCS AS THERAPEUTIC TARGETS

The different pharmacological or biological agents which are useful of IEC-DC interactions could be exploited to improve antitumor strategies or to control a variety of chronic inflammatory conditions. As we mentioned above, many factors including RA, TGF-β, IL-10 and TSLP contribute to tolerogenic DCs and Treg cells. Such as stable tolerogenic DCs had been obtained when DCs were treated with IL-10 [110]. RA produced by DCs promotes the conversion of naive T cells to Treg cells. So RA is an important regulator in intestinal immune cells. It promotes the difference of Treg cells and suppresses the difference Th1 and Th17 cells. RA can prevent Inflammatory Bowel Disease (IBD) and promote recovery of intestinal inflammation in vivo. In addition, RA has been successfully used in autoimmune diseases, such as experimental allergic encephalomyelitis. Now DC-based vaccines have used in cancer immunotherapy and have attained the goal of effective. Therefore target-gene therapy of tumors and

cancer with DC chemoattractants are currently pretty adjuvant therapeutic methods [111]. IEC-DC can promote the development of gut-homing Treg cells to protect against experimental colitis through potent suppressor activity. This will create a new situation for possible therapeutic intervention [95].

CONCLUSION

In this review, we conclude the interactions that occur during tolerogenic and immune responses depend on the crosstalk between IECs and DCs. This 'tight' crosstalk between IECs and DCs may regulate the generation of inflammatory responses to enteric bacteria. A better understanding of this fascinating interplay is needed before further therapeutic advances can be made.

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