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The Role of Intestinal Epithelial Cell Signaling In Mucosal Immunity

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Abstract: In the words of Hippocrates, all disease begin in the gut. In the intestinal lumen, there are more than 1000 species of microbiota members containing 600,000 genes. that is 10 times more than the number of nucleated cells in our body. Connections such as tight junction (TJ) and adherens junction (AJ) between epithelial cells prevent the passage of microorganisms and antigens to the lamina proprea, while transmitting the received stimuli with signaling mechanisms. Integrin and immunoglobulin like adhesion molecules, which are members of the tight junction, receive signaling with ErbB (Her1, EGFR/2/3) and cytokine receptors (transforming growth factor TGFβ receptors) and transmit them to the nucleus, creating signals for gene transcription, proliferation, differentiation, cytokine synthesis, synthesis of surface receptors, epithelial mesenchimal transition (Emt) regulation, or apoptosis and growth arrest. Tight junction transmembrane proteins, scaffolding proteins such as zonulin, communicate with afadin-mediated AJ, allowing signals to be transmitted to the cytoskeleton. It makes gene expression with the transcription factor to which it is attached. It contributes to the ion balance with claudin, cytoskeleton regulation with occludin, gene transcription and cytokine synthesis with Marveld3, from the members of the TAMPs family to which it is linked. The stimulated cell synthesizes Wingless-ınt1 (Wnt) signaling molecules and performs paracrine and autocrine signaling. It balances intracellular Ca^{+2} level with non-canonical Wnt pathway, provides cell polarity especially via Cell division control protein 42 (CDC42) with non-canonical polarity pathway, β-catenin mediated gene transcription with canonical Wnt pathway. While microbial antigens are recognized by Toll like receptors (TLR) and cytokines are synthesized, antigen molecule presentation is regulated by major histocompatibility complex (Mhc) molecules. Cytokines synthesized by signaling trigger innate immunity in the lamina propria (LP) and adaptive immunity consisting of $50x10^9$ lymphocytis, thereby initiating the anti-inflammatory or pro-inflammatory process. This review describes all these mechanisms and their connections.

Keywords: Tight Junction, Zonulin, CDC42, Gut Homing, B1 Lymphocytes

1. Introduction

Epithelial cells establish connections with each other and the subepithelial region through various proteins in dynamic structure. It is a selective permeable gate formation that separates tissue compartments from each other and from other tissue compartments. Apical and basolateral connections provide cell-cell adhesion; regulates paracellular selective permeability; provides polarization; transimitting informations between cytoskeleton, cell nucleus and other cells; It makes signaling networks that regulate cell behavior.

In particular, signals transmitted from the intestinal epithelium to the subepithelial area or antigenic stimuli create an immune response. It causes a local immune response along with an immune response directed primarily to the body. Epithelial cell itself is transformed by recognizing antigenic structures and supports immunity.

Our aim in this article is to draw attention to the fact that in case of any defect in epithelial junction proteins, mucosal immunity functions may be impaired and this may cause an abnormal immune response in the body with the gut homing mechanism that will be mentioned in the below. It has also been suggested that antigenic stimuli to the intestinal epithelium may trigger the underlying autoimmune disease through the gut homing mechanism.

2. Signalization at Tight Junction

Junctional adhesion molecules-A (JAM-A) protein is an immunoglobulin (Ig) like adhesion molecule and at the same time a transmembran adhesion molecule. The extracellular d1 and d2 subunit is similar to the immunoglobulin structure and a region in the d2 unit is called a trans region, this region is associated with the opposite cell JAMA trans region. A region of the d2 unit is also called the cis region; this region provides a connection with the same cell JAMA. Heterodimer integrins, which are transmembrane adhesion molecules, provide specific binding of cells to cell-cell, cell matrix and various ligands [1, 2]. integrins are effective in signal transduction, cell cycle, regulation, organization of the cytoskeleton. When the membrane receptors (ErbB, chemokine, etc.) with which it interacts are bound to the ligand, conformational change begins in the integrin. While the globular heads are inclined close to the cell membrane, the extracellular part elongates in response to changes in the cytoplasmic tail, the heads move away from the membrane, the ligand affinity increases. This is called inside-out signaling. Membrane receptors further increase the binding strength by enabling integrins to aggregate [1]. When vitronectin (ligand of αvβ3) or the RGDS (arg-gly-asp-ser) motif (ligand of α5β1) binds with the ligand, integrin molecules interact with tetraspain the cell surface glycoprotein cluster of differentiation-9 (CD9) [3]. Exosome is present in the intracellular portion of CD9. While ErbB1 receptors such as epidermal growth factor (EGF) receptors, which interacts with integrin, bind with its ligand. The same ligand interacts with integrin at the same time and provides internalization. On the other hand CD9 increases the adhesion capacity by including the Ig like adhesion molecule in the complex with indirect interaction [4]. In addition a disintegrin and metalloproteinase ADAM 17 provides negative regulation by shedding of adhesion molecules by connecting with CD9. When CD9 increases, shedding with ADAM 17 is reduced and adhesion is maintained [4, 5]. The monomeric JAMA leaves the complex and interacts with the other JAMA in cis. Focal adhesion kinase (FAK) in the cytoplasmic extension of integrin is activated through disruption of the auto-inhibitory intramolecular interaction between the FERM domain and the central kinase domain. The FERM domain binds both with integrin and ErbB and Src family kinases, which initiate the downstream signaling pathway through phosphorylation, are released and form a complex with Shc transforming protein-growth factor receptor bound protein (Grb) 2, phosphoinositide 3 kinase (PI3K) [6]. If the P110 p85 isoforms of PI3K bind to the Shc-Grb2 complex, it converts the phosphatidylinositol bis phosphate (PIP2) to phosphatidylinositol triphosphate (PIP3) and the phosphainositide dependent kinase (PDK) is taken to membrane. It activates the mammalian target of rapamycin (mTOR) protein kinase with protein kinese b serine/threonine kinese (PKB/AKT) phosphorylation. Phosphatase and tensin homolog (PTEN) suppresses PI3K activation and prevents excessive akt protein kinase activation, thus protecting it from carcinogenic effects.

The Gαs protein family bound to ErbB receptors, it stimulates adenylate cyclase, increasing cyclic adenosine monophosphate (cAMP) synthesis and activating protein kinase A (PKA) [7]. cAMP elevation activates evolutionarily conserved RAP1-GEF and converts RAP1-GDP to RAP1-GTP [8]. It supports the internalization of integrin in interaction with ErbB, supports signaling pathways by modulating the intracellular Ca^{+2} level [9]. Dimerized JAMA; It forms complexes with RAP-GEF, ZO-2, AF6 and controls the contraction of the apical cytoskeleton, and regulates epithelial permeability [10].

If son of sevenless (SOS)-guanine nucleotide exchange factor (GEF) is bound to the Shc-Grb2 complex, the RAS-GDP turns into RAS-GTP, activating the mitogen activated protein kinase (MAPK) pathway. ERK1/2 is activated via MKK and provides proliferation, cell division, differentiation [11, 12]. If this pathway is stimulated by hyperosmosis, oxidative stress, uv radiation, heat shock proteins, lipopolysaccharides, inflammatory cytokines (IL-33, TGFβ, TNFα) [13], c-Jun N-terminal kinase (JNK) stimulates AP-1 transcription factor and expression of the GM-CSF, IL-8 and chemokine ligands such as CCL5 [14]. If this MAPK pathway stimulates p38 mitogen protein kinase, many pro-inflammatory cytokines TNF-α and interferon (IFN)-γ are synthesized via the nuclear factor κappa B (NF-κB) [15].

In addition epithelial regeneration occurs with the transcription enhance associated domain (TEAD) transcription factor by the Hippo pathway, via yes-associated protein (YAP)-transcriptional coactivator with PDZ –binding motif (TAZ). YAP-TAZ molecules bind to TJ, AJ and the polarity module. There is no YAP in the mature organ; it occurs in damage, stress, and injury with nutrients; it is organ-specific. YAP-TAZ acts by binding to β-catenin in the canonical Wnt pathway [16]. Fetal markers Anxa1, Trop2 and Sco1 appear; YAP is activated; the stem cell proliferates. When the injury is resolved and RhoA combines with the cell membrane, proliferation stops with its effect on LATS kinase and apical polarity module [17]. Adult cell fate is loaded back into the cell with YAP-TAZ [18, 19]. YAP-TAZ is also inhibited by zonulin-1 (zo-1) and zo-2. When zo-1 is shedding by ADAM 17 from the JAMA-CD9-integrin complex [8], YAP-TAZ inhibition is lifted. YAP-TAZ activation involved etiology of ischemic heart disease and dilated cardiomyopathy [20]. The presence of zo-1 shedding has been shown in celiac disease and dilated cardiomyopathy seen in celiac disease may be caused by this mechanism. [Figure 1].

2.1. The Importance of Zonulin in Signalization and the Connection of Tight Junction and Adherence Junction

Many transmembrane proteins are attached to the cytoskeletal structure by scaffolding proteins called zonulin. Zo-1 is containing 3 PDZ domains; SH3 and GUK domains and C- and N- terminus. it is stabilized to the membrane by the chlorine channel membrane protein CFTR [21, 22]. The N-terminus of zonulin-1, zo-2, zo-3 is in the same structure;

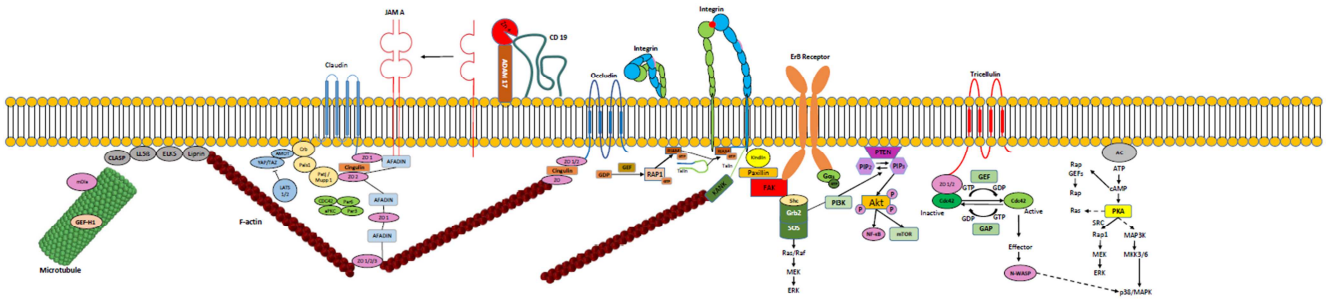
while the C-terminus is unique and tissue-specific response with alternative splicing. Zonulins communicate with each other via the 2.PDZ domains. zo-1 in the membrane, zo-2 in both the membrane and the nucleus is found. Zonulin-3 has been shown to compensate for the zo-2 deficiency [22].

The 1.PDZ domain of zo-1 interacts with claudin; 3.pdz domain of zo-1 interacts with JAMA and tricellulin; SH3 domain of zo-1 interacts with afadin (AF6) and ZO1-associated nucleic acid binding protein (Zonab); GUK domain of zo-1 interacts with occludin, α cathenin and tricellulin; all zonulins bind to actin via their C-terminus (10. Zo-2 and zo-3 interacts with claudin [22]. The blood vessel epicardial substance (BVES) is connected via the zo-1-Zonab-GEF complex.

Zonab is a transcription factor found in TJ and nuclei; regulates transcriptional factors and post- transcriptional regulatory genes [23]. It provides the expression of the head shock protein APG2. It increases TJ permeability by suppressing claudin and occludin protomers [22].

AF6 takes place in the E-caterin-cathenin complex and it binds nectin (an immunoglobulin like adesion molecule) to actin which are AJ members [21, 24, 25]. The zo-1 GUK domain forms a complex with α-cathenin so connects the AJ [26]. TJ and AJ communicate through AF6 and zonulin communication.

Claudin is a transmembrane protein in the form of 4 antiparallel helix bundles, its homo/heterotypic structure regulates tissue-specific ion passage. Claudin5 is most common in the epithelium [27]. Claudin binds to zonulins. When transmembrane proteins are stimulated, they stimulate zonulin and afadin, which they interact with, and activate the ion channel claudin which they are attached. [Figure 1].



signaling assembly resulting from tight junctions and adhesion junctions with stimuli

Figure 1. *Intestinal epithelial cells.*

2.2. Wnt Pathway

Evolutionarily conserved Wnt signaling molecule from different cell populations, which remotely influences the signal transduction of neighboring cells, is released out of the cell in lipoprotein bound or free form [28, 29]. Thus, it notifies the neighboring cells of the incoming warning. [Figure 1].

2.2.1. Non-Canonical Wnt / Calcium Signaling Pathway

Non-canonical Wnt / Ca^{+2} signaling pathway ROR-cell specific frizzled (FZD)-diseveled (DVL)- Wnt pathway regulates intracellular Ca^{+2} level [29]. This pathway is stimulated by the free form Wnt molecule. While regulating the Ca^{+2}, it stimulates adenylate cyclase by interacting with the Gαs protein family, which is connected intracellularly to FZD, similar to ErbB receptors and activates PKA by increasing cAMP synthesis [30]. PIP2 is hydrolyzed by phospholipase c (PLC) to form diacylglycerol (DAG), while inositol triphosphate (IP3) is released. IP3 binds to its receptor at the endoplasmic reticulum (ER) and increases the release of Ca^{+2}. DAG combines with the Ca^{+2} coming out of the ER to form CALDAG-GEF and provides Ca^{+2} balance with the activation of RAP1-GEF. Increase in Ca^{+2} in the cytoplasm, increases the activity of protein kinase C (PKC), Ca^{+2} calmodulin dependent kinase (CAMKII), calcineurin (CaN) [31, 32]. If the Ca^{+2} release from the ER is insufficient, it supports the intake of Ca^{+2} into the cell through the Ca^{+2} channels called ORAI-1, mediated by the stromal interaction molecule-1 (STIM1) on the ER [33]. While CaN directly enables the transcription factor nuclear factors of activated T cell (NFAT) to enter the nucleus from the cytoplasm, activated PKC and CaMKII transcribe the gene via nuclear factor κB (NFκB) [34]. While pro-inflammatory and anti-inflammatory cytokines are synthesized by this pathway, it stimulates the production of thymic stromal lymphopoietin (TSLP), an important cytokine for inflammation [35]. P120-cathenin in the intracellular part of the ROR is released to join the non-canonical planar cell polarity Wnt pathway.

2.2.2. Canonical Wnt Pathway

The Canonical Wnt pathway is stimulated by the Wnt signal molecule released in conjunction with the lipoprotein. Lipoprotein receptor-related proteins (LRP)- FZD-DVL is joined by the glycogen synthase kinase 3 β (GSK3β)-Axin-βcathenin-adenomatous polyposis coli (APC)-CK1 cytoplasmic complex [36, 37]. With the stimulation of Wnt-Fzd, LRP5/6 is bound with Src and E-catherin. E-catherin interacts with β/α-cathenin, which closes p120 cathenin and vinculin binding domain to the interact with actin cytoskeleton [38, 39]. The tyrosine residue of β-cathenin is phosphorylated by Src. Protosome ubiqutin-mediated β-cathenin leaves the complex and enters the nucleus when β-cathenin phosphorylation stops [36, 40, 41]. β-cathenin goes to the nucleus; it is synthesized c-myc, cyclinD1, Axin2,

Dkk1 proteins via TCF/LEF and LGR5+ stem cell synthesis is supported by leucine rich repeat containig G protein coupled receptor 5 (LGR5) gene transcription; IL-6, IL-8, TNF α synthesis is stimulated for inflammation [40, 41]. CAMKII regulates the nuclear activity of β-cathenin [31].

TAM receptors member Tyro3-Axl-MerTK drives a pathway similar to the Wnt signaling pathway [42]. A signaling pathway similar to Canonical Wnt is the Hedgehog pathway.

2.2.3. Non Canonical Planar Cell Polarity Wnt Pathway

CDC42 has assumed the main regulatory role for this pathway. CDC42 protein mechanism comes into play both with the effect of p120-cathenin and Ca^{+2}. CDC42 complexes with tricellulin (member of tams family, contains marvel domain, found in bicellular junctions), tricellulin-linked zo-1, TUBA-GEF, and serine/threonine protein kinase Pak4, is involved in TJ [43]. CDC42 is associated with the apical polarity module (Par3-Par6-aPKC), which has a critical role in actomyosin activity. CDC42 converts GDP to GTP with Tuba-GEF in its complex form [44]. By phosphorylating PKC in the apical polarity module, it separates Par3 from the complex and leaves it in the apicolateral membrane [45, 46]. On the other hand, Par6 forms a complex (Crb3, Pals1, PatJ, Lin7) with another polarity protein, crumbs 3 (Crb3), a polarity module member associated with Ig-like adhesion molecules, and migrates upwards to the apical membrane [47]. Par3 contains Pdz domains; 1.Pdz binds with Par6, JAMA and nectin, 2.Pdz binds with phosphatidyl inositol lipid, 3.pdz binds with Pten and cadherin [2, 48].

Jama-associated Par3 becomes phosphorylated, it phosphorylates GEF, which is connected to the microtubule from its N-terminus. GEF is released, which stabilizes the microtubule (MT) by acetylating [49, 50]. TUBA binds to N-Wasp and supports actin polymerization via GTPase. Active GEF converts Ras homolog family member A (RhoA) GDP to Rhoa GTP. RhoA is the main regulator of actin [51]. It creates stress fibers and contracts the cell.

mDia, another factor that keeps MT stable. When MT depolarizes with the activation of mDia, the GTP-tubulin and the end trafficking protein (Tıps) complex are separated at the MT end and MT end is opened [52]. The MT stabilizer Liprin-Elks-Erc1-Ll5β and the family of CLASPs fixes the tip of the microbule into the tight junction [44].

Par3 mediate aktive RhoA collects Fak into the integrin intracellular portion. Integrin stabilization increases with Fak-Src aggregation. İntegrin and talin, vinculin and paxillin bind via kank protein to the membrane [18].

Another member of the Wnt pathway is Ras related C3 botulinum toxin substrate (Rac1) forms lamellipodia with activation via αvβ5 integrin and protrudes into the shape of the foot against the stimulus, while filidopodias are formed via CDC42 and grasp the agent with fingerlike protrusions. α4β1 and α5β1 regulate lamellipodia movement.

The chemokine receptor synthesized in the inflammatory process also strengthens the tension by enabling talin to join the cytoplasmic formation of talin through the adaptor protein Rap-1 interacting adaptor protein (Riam) [53].

2.3. The Place of Tamps Family Members in Signalization

Tamps family members located in TJ are tetraspain proteins containing marvel domain consisting of occludin and tricellulin located in bicellular junctions and marvelD3 in tricellular junctions. Marvel domain is the name of Myd88 adapter like protein (Mal) and releated protein for vesicle traficciking and membrane [54].

Occludin and claudin binds to the zo-1. It binds to other zonulins via Cingulin-Paracingulin and Jacop [48]. The amount of occludin does not change with stimulation, it is mobile. The TGFβ receptor supports this complex [48]. Occludin-linked complex is associated with F-actin mediated zonulin. Activates ROCK and LIMBK via the p114RhoGEF (the name of Cingulin adaptor protein Rho GTPase-GEF) [47, 48, 55]. While GEF provides actin polymerization by activating RhoA, activated ROCK activates myosin filaments [56]. and balances gene expression and cell differentiation in the nucleus. This activation increases paracellular permeability by internalizing the occludin. Inhibition of Wnt signal or IL-4, TNFα, IL-6 increases claudin and occludin synthesis via ZONAB and regulates paracellular permeability [57].

Tricellulin taken into TJ with CDC42-TUBA-GEF acts as a receptor for LSR (angulin1), ILDR1 (angulin2), ILDR2 (angulin3) and apolipoprotein b/e; provides clearance of chylomicron and LDL [58]. Tricellulin produces transcription factors in the nucleus via CDC42 signaling.

MarvelD3 is associated with occludin or tricellulin in the tricellular junctions. It internalizes with the endosome. When tricellulin or ocludin is activated, it activates the MAPK pathways.

BVES has a Popeye domain in the intracellular domain. It interacts with Occludin and acts on cAMP, acts through the Zonab [59].

3. Antigen Presentation by Mhc via TLR

Antigenic structures are recognized to TLRs that are members of the recognizing pathogen associated molecules pattern in the epithelial cell. There are TLR4, TLR 5, TLR 11; TLR 1 and 2 and TLR 2 and 6 in complex in the cell membrane. While complexes recognize lipoprotein, lipoteichoic acid, peptidoglycan and zymosans; TLR 4 recognizes lipopolysaccharide and viral protein; TLR 5 recognizes flagella. TLR 2 and 4 of these contain the MD2 subunit, increase synthesis of inflammatory cytokines by MyD88-TRIF, IKK-TBK1, NFκB-IRF3. Stimulation of other cell membrane-bound TLRs results in MyD88-mediated activation of IRAK4-IRAF6 and IRAK1-TRAF6, phosphorylation of IKKa-IκBkinase, and NFκB binding to DNA for proinflammatory cytokine synthesis. These cytokines control the gene region with negative feedback. TLR 7/8/9 and MyD88 independent TLR 3 are found in the nuclear membrane. [60]. TLR 9 also includes the MD2 subunit. TLR3 recognizes dsRNA, TLR 7 and 8 recognizes ssRNA, TLR 9 recognizes Cp6DNA virus, bacteria, nucleic

acid, endosome. Parasites provides TNF-α, IFN-γ, IL-10, IL-12, TGF-β synthesis via TLR [1, 61].

The epithelial cell can present the antigenic epitops with both MHC1 and MHC2 [1]. All nucleated cells are divided into 8-11 amino acid peptide epitopes by the protosome in the cytoplasm, loaded into MHC1 β2 microglubulin in the ER, sent to the cell membrane by golgi and presented to CD8+ T lymphocytes in the LP. MHC2 which is synthesized in an invariant chain-linked manner in the ER, comes to the cytoplasm and is clipped with HLA-DM and the antigenic epitope is loaded. Antigen is vesicled with a phospholipid layer from the cell membrane and divided into peptides of 10-30 amino acids with proteolytic enzymes, presented to CD4+ T cells. It has been shown that microbiota is disrupted with a high-fat diet; TLR is decreased and MHC2 presentation is [62, 63].

With TLR 4 and 5 stimulation, transmembrane protein Fas and Fas ligand expression increases, triggering apoptosis in the epithelium [64, 65]. However, the secretion of cytokines APRIL and BAFF from the epithelial cell to the LP is also supported.

4. The Place of Cytokine Receptors in Signalization

TGFβ is a serine/threonine kinase receptor that provides ligand to integrins by synthesizing fibronectin and plasminogen activator inhibitor-1 (PAI-1) [66]. It increases fibronectin synthesis by activating Jnk/Sapk and Mekk1/Mkk4, Jnk cascade, Smad pathway [67].

IL-22 acts specifically on Paneth cells. Wnt and Notch signal inhibition makes stat activation. Intestinal stem triggers change from cell [68].

TNFα down-regulates the target genes of NFκB, while IL-10 positively regulates the canonical NFκB signal [69].

5. The Importance of the Emt Mechanism

Coxsakie and adenovirus receptor (CAR) Ig-like adhesion molecule in epithelial cell membrane provides gene transcription via Notch signaling. Notch is an epidermal like growth factor like transmembrane receptor. Notch has delta-like (Dll) and jagged (Jag) ligands. It increases the expression of MHC2 especially with the Dll-1 ligand [70]. The Car and Notch complex ectodomain undergoes shedding with Adam-10, the intracellular domains of Notch and the amyloid precursor protein go to the nucleus, modulating gene expression [71]. Notch signal also makes Emt especially through NFκB such as Wnt pathway, Hedhehog pathway, TGFβ, ErbB, Bves [72]. In addition, Gata4 signal containing zinc-finger in the small intestine increases the expression of DII1 while supporting Emt over Srp [73]. Epithelial cell transforms into mesenchymal stem cell. It migrates to the LP with lamilopodia and filidopodia forms, which are shaped by actomyosin activity as a result of the signals formed.

Mesenchymal cell is an adult type stem cell. These mesenchymal cells are a source of self-renewing, differentiating, immunomodulatory, puliripotent T cells. Loss of mesenchymal cell apicobasal polarity; e-catherin, claudin and desmosome transcription reduction; starting the synthesis of N-catherin, vitronectin, fibronectin. Mesenchymal cell contains anti-inflammatory CD73 for T cell, Thy-1 pan T cell indicator CD90, TGFβ receptor CD105. While cell-cell acts directly with adhesion, it has a paracrine effect by secreting secretomes. Generally potentiates the anti-inflammatory response [74]. It converts macrophages to the anti-inflammatory M2 form, increases TGFβ secretion from macrophage and converts other T-cells toT regulatuar (Treg). It also regulates the expansion of B cells and antibody synthesis [75, 76]. IL17 and IL-22 decrease, increase TGF β, IL-10, PGE2 and IFNγ. This mesenchymal cell synthesizes high levels of PD-L1 /2 and arrests T cell proliferation. The monocyte chemotactic protein Mcp-1 secreted, it stimulates Fas ligand synthesis in T cells and increases T cell apoptosis.

These mesenchymal cells may be T-cell precursors in the gut.

6. T Lymphocyte Development

In the embryonic period, T lymphocytes migrate from the bone marrow to the thymus with Gata3 signal and enter the thymus from the corticomedullary junction. Self antigens are introduced to these T cells by Mhc1 and Mhc2s by macrophages, dendritic cells, and thymic epithelial cells. T lymphocytes entering the thymus as double negative (Dn1) (CD44+ CD25-) become Dn2 (CD44+CD25+), then Dn3 (CD44-CD25+) with Notch1 signal. Then, in the Pre-TCR stage, while the TCR pre-α is formed, the β gene rearrangement is recombined with the Rag1 and Rag2 genes. In particular, it has been shown that β selection for αβT lymphocyte TCR is mostly regulated by Tcf1/Lef1 transcription factors activated by canonical Wnt pathway [77, 78]. Then, it was shown that the step in which α gene rearrangement was performed while double positive was regulated by PI3K/AKT/mTor. Then the T lymphocyte goes to the central tolerance level. TGF β family (Activin, Inhibin, TGFβ, BMP) signaling pathways are also effective for αβ and γδ lineage selection [79]. BMP4 is effective in γδ T lymphocyte production [78]. Notch ligand Jag2 also supports γδ T cell, Jag1 supports αβT cell, Notch1 supports both series, while Notch3 supports γδ T cells [80]. In addition, TSLP synthesized from thymic epithelium and medullary thymic epithelium performs thymopoiesis; increases DN1 and DN2 progenitors; increases the number of naive T lymphocytes; induces CD4+T expansion and CD8+T differentiation; especially triggers the formation of Treg. TSLP increases B lymphocyte precursors from the fetal liver; triggers CD11c DC maturation [81].

All signaling pathways involved in T cell development in the thymus are also present in the gut. Just like the cells that come to maturation from the bone marrow to the thymus, the source cell in the intestine may be mesenchimal cells that

come to the LP by Emt. Unlike other tissues, the presence of GALT in the LP may contribute to its being an alternative T cell development site. Also an important point is that in the absence of an inflammatory agent, classical tissue DCs present self-antigens to self-reactive T lymphocytes without generating a pronounced cytokine and costimulatory response. Activated classical tissue DCs cause T lymphocytes to die, inactivate or transform into Treg cells. Thus, self-tolerance is achieved. However, during the development of T lymphocytes in the thymus, self-reactive T lymphocytes are killed and prevented from going to the periphery by negative selection [1]. Presence of self-reactive T cells in the gut may suggest that these T lymphocytes develop in the gut. CD105 may drive the γδ T cell direction. Based on this, it can be thought that the T cells found in Digeorge syndrome with thymic aplasia may originate from the intestine.

While Mhc1 is expressed in intestinal epithelial cells, Mhc2 is expressed in response to IFN-γ (1). However, this Mhc2 is not efficient at processing protein antigens as peptides and generating T cell response and does not express costimulators. This may suggest that Mhc2 in epithelial cells may play a role in antigen presentation to T lymphocytes for the development of new T lymphocyte lineages with limited antigen specificity in response to angiogenic structures in the microbiota which are probably found in the gut [1, 82].

7. Interaction in the Subepithelial Domes and the Lamina Propria

7.1. Function of B1 Lymphocyte

Among the epithelial cells, in the follicle-associated epithelium, there are microfold (M) cells derived from LGR5+ stem cells in the crypt epithelium. It passes very low molecular weight antigens by absorptive transcytosis. It does not present antigen with Mhc. The basolateral part of the cell is concave, reducing the distance of transcytosis. The antigenic structure reaches the mature B-1 lymphocytes which are originating from the fetal liver located in the subepithelial dome (SED) in the basolateral pocket of the M cell [57]. CXCR4 is found on the B1 lymphocyte surface and synthesizes CCR1, CCR6 when stimulated by antigen. It can present the antigenic construct to Cd11bCd18 DCs expressing αvβ8 or deliver it to the germinal center of unencapsulated Peyer's patches, particularly in the ileum. B1 lymphocyte migrates to reticulum cells that have CXCL12, the ligand of CXCR4 on its surface. In the presence of TGFβ, it stimulates IgA class swicthing from B lymphocytes [83]. It can decrease CCR6 and get out of peyer patches.

CCR6 expression is increased on DC and macrophage surface in inflammatory state. IL1β and TNFα proinflammatory cytokines synthesized by macrophages stimulate the cytokine receptors of the basolateral membrane of the epithelial cell via NFκB, increasing the synthesis of CCL20, the ligand of CCR6 and chemotaxis for innate immune response cells. In addition, it supports the signaling pathway by increasing the CCR6 on the epithelial cell apical surface and increasing the signals from the ErbB receptor.

B-1a CD5+, IgM+, IgD are low. B-1b is CD5-. It is thought that marginal zone B cells in the spleen may originate from the peritoneal region [1, 84]. B1 cell B cell receptor (BCR) is self-reactive, synthesizing antibodies in response to microbiota and self-antigens. It is the source of natural IgM in steady state. Even if it has not encountered antigen before, it provides protective natural IgM synthesis. About half of the IgA-secreting plasma cells in LP are derived from B1 cells [1]. While IgA class switching occurs in the germinal center of peyer as TGFβ-dependent and T-independent via B2cells; IgA class switching may be occur T-dependent via B1 lymphocytes.

The B lymphocyte expresses CCL9 and attracts DC to the M cell region [85]. As a result, the M cell provides basal IgA synthesis with commensal bacterial antigenic stimulation. However, exposure to commensal microorganisms in the early stages of life is required for the formation of B1 lymphocytes. Otherwise, it has been observed that the B1 response is impaired and shifted to the B2 lymphocyte response, which initiates the autoinflammatory process and creates food allergies [57].

Like fetal liver-derived γδT lymphocytes, B1 lymphocytes has a limited variety of antigen receptors (1). When the BCR on the surface of B1 lymphocytes binds with the antigen, the signaling occurs and NFkB induction decreases, Scr/Lck act and proliferation is inhibited. This process produces anergic B2 lymphocyte-like effect. B1 cell ynthesizes IL-3, IL-10 and GMCSF; it has an anti-inflammatory effect in steady state; prevents tissue damage. It binds to self-antigens that appear in injury and suppresses the Teffector response. When the BCR and its costimulator on the surface of B1 lymphocytes binds with the especially with oligosaccharide and peroxidation-oxidized lipid antigen (oxldl), AKT phosphorylation occurs via PI3K, and MHC2 increases rapidly and strongly, initiating an inflammatory response in a T-independent manner. This process functions like activated B2 lymphocyte [57]. Lipopolysaccharide stimulation promotes IgA switching [86]. Even if there is no antigenic stimulus, it is long-lived, self-renewing in its own pool, but its amount decreases with age [84].

B1 lymphocyte undergoes positive selection with central tolerance during its development in the neonatal period, that is, those that recognize its own Mhc are selected. Then, while those that are self-antigen-reactive are killed by negative selection, B1 cells do not enter the negative selection mechanism and continue to live as self-antigen-reactive [57]. Being self-antigene reactive may support phagocytosis of apoptotic cells, enabling it to function for organ sheping in the neonatal period. Apoptotic cell does not present antigen, it signals apoptosis with phosphatidylserine surfaced by flip flop. It has been shown that oxldl lysophosphatidylcholine is also presented in apoptotic cells and reacts with self-reactive B1 cells. [Figure 2].

7.2. Function of Intraepithelial Lymphocytes

Antigenic stimulation causes IFNγ expression from

intraepithelial γδT (TCR containing CD3 and ζ protein), CD8αβ T and CD8αα T lymphocytes. With the effect of IFNγ, Mhc2 presentation from the crypt cell increases [1, 72]. In general, T lymphocytes can recognize and respond to the antigen presented by antigen presenting cells (APCs) with Mhc in the presence of costimulators. CD8αβ T and CD8αα T lymphocytes respond to Mhc1-presented antigens and show cytotoxic effects. While γδT lymphocytes can recognize small phosphorylated molecules, alkyl amines, and lipids presented by Mhc1; it can recognize protein and nonprotein antigens without APC and Mhc, possibly by activation by cytokines synthesized from epithelial cells or by Wnt pathway signaling or microbial heat shock proteins. It synthesizes proinflammatory IL-17 [1]. Intestinal epithelial cell also synthesizes TSLP basally [87]. Transgenic expression of TSLP promotes γδ T cells [78]. There are Vγ5 γδ T lymphocytes in the human gut. αEβ7 integrin found in epithelial γδ T cell binds with E-catherin in epithelial cell. In the presence of TGFβ, T cell receptor (TCR) located on γδT cell binds to epithelial CAR [88, 89]. MAIT, which also contains semi-invariant TCR, is located in the intestinal region. [Figure 2].

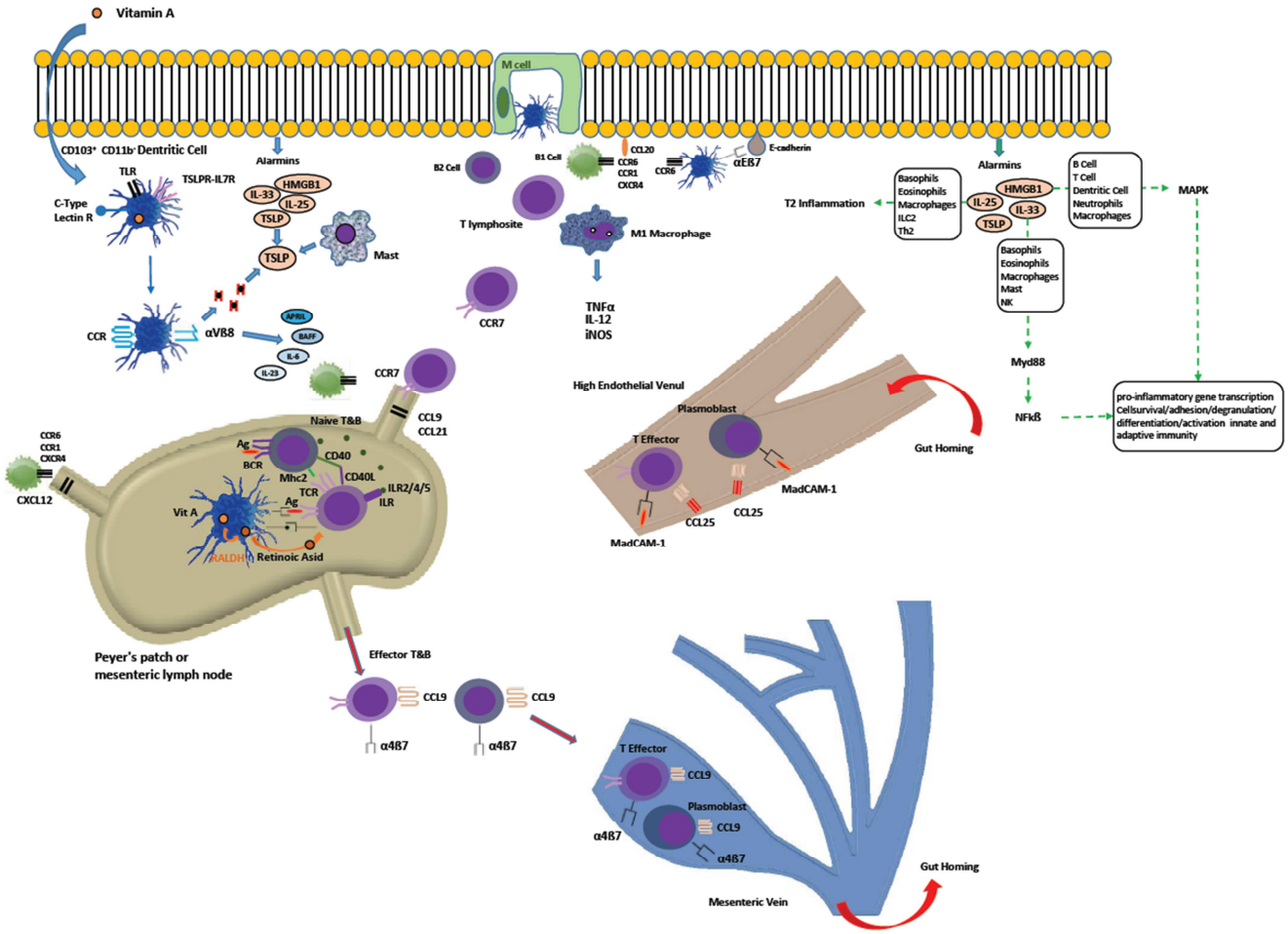


Figure 2. *Direction of mucosal immunity in the lamina propria of alarmins formed by stimulation of intestinal epithelial cell and antigenic structures transferred to the subepithelial dome.*

7.3. The Role of Alarmin and Innate Lymphoid Cells in Mucosal Immunity

Proinflammatory cytokines are released into Sed by gene transcription and translations that occur as a result of the above-mentioned signaling mechanisms in the epithelial cell ecpecially Nfκβ. Cytokines such as HMGB1, IL-1 α, IL1f7β, IL-16, IL-25, IL-33, TSLP called alarmin, trigger the immune response [90].

Innate lymphoid cells in the LP which are considered the innate counterpart of T cells, which play a key role in mucosal immunity, are triggered with alarmins. ILCs vary according to localization in the gut, age, and circadian rhythm. Since it does not contain the RAG gene, it does not have rearranging antigen receptors. They do not contain TCR but contain myeloid and dendritic cell markers.

ILC1 differentiates with TGFβ signal and synthesizes IFNγ, granzyme and perforin. It triggers phagocytosis and increases the formation of oxygen radicals. It triggers type 1 immunity [91].

ILC2 differentiates from ID2 by activating Gata3 signaling by IL-7 and increases IL7Ra expression [1]. It synthesizes IL-4, IL-5, IL-9, IL-13 with the effect of IL-25, IL-33 and TSLP [91]. TSLP is secreted from DC and mast cells by the

effect of alarmin APRIL, which is synthesized as a result of stimulation of the epithelial cell with TLR, or by external administration of isoretinoin. Increased Cd45Ro+ combines with IL2α synthesized from tissue resident Tmemory cells to induce ILC. It protects B1 cells with IL-5 and turns CD4+T cells into Th2 effectors. With IL-13, it increases the synthesis of mucus, which is a single layer in the small intestine and a double layer O-bind oligosaccharide in the large intestine from the goblet cells [90]. It triggers type 2 immunity.

ILC3s differentiate from ID2 by RORγδ signaling under the influence of IL-7. Synthesizes IL-17, IL-22, GMCSF with the effect of IL-1β and IL-23 [1, 91]. It increases acute inflammation by synthesizing IL-17. It increases antimicrobial peptides such as α-defensin and trypsin in small intestine and β-defensin in large intestine by acting on paneth cells with IL-22. It triggers type 3 immunity.

The lymphoid tissue inducer (LTi), a part of the ILC3 group, stimulates their production by retinoic acid, macrophage-derived CXCL13, RANK-L, and cytokines IL-1β, IL-23, IL-6. It produces IL-17 and IL-22. It regulates autoimmunity and CD4 ensures the survival of memory cells. [Figure 2].

7.4. Adaptive Immunity Response with Antigen Presentation

The antigenic structure transmitted from the epithelium to the Sed enters the cell with nonspecific pinocytosis. Fluid antigens are binding to the c-lectin membrane receptor, protein antigens are recognized by TLR and other innate pattern recognition receptors in CD103+DCs (contains αEβ7. It binds to E-catherin. Thus, it can activate the Wnt signaling pathway). It matures with TNF, decreases the number of Fc receptor for mannose receptors and loses its stickiness. It goes to peyer's patches or mesentery lymph node by synthesizing the chemokine receptor CCR7, which is the receptor for CCL9 and CCl21 synthesized in lymph vessels in the lymph node. Since naive T lymphocytes synthesize CCR7, migrate to the same region. DCs secrete TGFβ, while Mhc2-dependent antigenic epitope is presented to naiveT and naiveB cells with the effect of IFNγ. With the effect of IFNγ and IL-4, B lymphocytes present antigen to CD4+ Thelper lymphocytes with costimulators in the mesentery lymph node, while B1 cell can present antigen in peyer's patches. APC receives signals such as IFNγ from antigen-presenting cells that increase antigen presentation and costimulator synthesis. T cell recognizes non-soluble, cell-associated antigens, short linear peptides; The B cell can recognize soluble, cell-free, folded intact peptides, nucleic acids, carbohydrates, lipids, small chemicals, antigens.

Especially in the terminal ileum, DC cells which are macrophage-derived and carry CXCR3, can extend their dendrites among epithelial cells and sample the luminal content. The most important feature is that it can provide the re-production of the junctional proteins that it degrades. This is a pathway that can be investigated therapeutically in permeable bowel diseases. CXCR3+ DCs present antigen to mobile DCs in Sed.

While APC presents antigen to the T lymphocyte, its TCR first recognizes Mhc and then the antigen. While ICAM-1 binds to LFA-1, the MHC of the antigen-presenting cell binds to the T cell CD4 or CD8 /TCR/CD3 complex, resulting in the first signaling, activation begins with prematuration. In the primary interaction phase, IL2Rα interacts with IL2Rβ; while CD28 interacts with CD80 (B7-1)/86 (B7-2) to survival. Class switching is performed by interacting with CD40 on the T lymphocyte surface and CD40L of the B cell. Then, in the differentiation phase, there is occur clonal expansion of different T cell subsets with different cytokines. If PD1-PDL1 interaction occurs, anergy develops. Transformation to Th1 is provided by IL2 and IFNγ, and it is involved in the etiology of inflammatory disease. Transformation to Th2 is achieved with IL-4, IL-5 and IL-13, it is involved in the etiology of allergic disorder; Increases mucus secretion, increases motility. The inflammatory process is triggered by conversion to Th17 with IL-6 and IL-17. In the small intestine, the mucus is a single layer and commensal bacteria come into contact with the mucosa. Thus, while commensal bacteria triggers the formation of Th17 while in a steady state, this Th17 increases the risk of autoimmune diseases outside the intestine. Treg CD25+, CD4+FoxP3+ T cell develops with TGFβ, IL-10, IL-6 [1].

8. Mechanism of Gut Homing

Vitamin A, which comes from the intestinal lumen with the diet, is delivered to Sed. Here, vitamin A is converted to retinoic acid by retinal dehydrogenese (RALDH), which is only found in the intestine, in DC via TSLP synthesized from epithelial cells. DC also synthesizes TSLP. Retinoic acid formed in DC ensures the expression of α4β7 integrin and CCR9 chemokine receptor in effector T cells and plasma cells. The stimulated lymphocytes first leave the intestine through the postcapillary venules to 'gut homing'. It circulates throughout the body and looks for the antigen presented to it in the body. MadCAM1 which is the ligand of α4β7 in the high endothelial venule and CCL25 which is the ligand of CCR9, return to the intestine and T cell act as a T effector, transform into B cell plasma cell and synthesize antibodies [1]. Since there is no RALDH in other tissues, it can be thought that RALDH inhibition can prevent 'gut homing' and prevent inflammatory bowel disease. Oral inoculation produces gut-homing IgA-producing B-cell expansion. B cell 'gut homing' in the colon occurs through the interaction of CCR10 and CCL28. This receptor and its ligand are also present in other tissues. For example, in asthma, CCL28 is stimulated by IL7A in the lung. IgE-secreting B cell carrying CCL10 to the lung increases migration to the lung [92]. From this point of view, it can be thought that orally administered vitamin A to protect against bronchopulmonary dysplasia removes plasma cells carrying CCR10 from the intestine by 'gut homing' and directs them to the lung where its ligand, CCL28, is located. These B lymphocytes may regulate the remodeling of epithelial cells by secreting IgA in the lung.

9. Class Switching Mechanism of B Lymphocyte

In the intestinal region, mainly class switching occurs by a T-independent mechanism with TGFβ released from intestinal epithelial cells and DCs expressing αvβ8. Treg transformation from CD4+T cells is triggered, Th1 and Th2 are inhibited. DC supports class switching by synthesizing nitric oxide (NO) and all-trans retinoic acid. It has been shown that TGFβ1 is secreted from the epithelium to the LP with the signals that occur when integrin is stimulated with RGDS [79]. For example, short-chain fatty acid which formed by the microbiota and found in breast milk, has been shown to increase TGFβ1 synthesis from intestinal epithelial cells. [93]. So short chain fatty acids seem to support class switching. Based on this, the short-chain fatty acids in breast milk providing active immunity against infections by increasing the secretion of IgA in the intestine. On the other hand can be said that it regulates the homeostasis of the response to newly encountered antigens by triggering thymic Treg expansion, reducing systemic neutrophil and macrophage response, regulating antiviral macrophage, DC, NK functions, and inhibiting eosinophil effector functions. Secreted IgA binds to the glycoprotein polyimmunoglobulin receptor located on the basolateral membrane of the intestinal epithelium. It increases in case of inflammation. It binds to form of a dimer IgA and is taken into the cell by endocytosis. It is sent to the intestinal lumen by complex transcytosis. It undergoes proteolysis in the lumen, its transmembrane and cytoplasmic part is separated; cellular domain complex with IgA remains. This secretory complex protects IgA from proteolysis. IgM is also secreted in small amounts by the same receptor. In the rectal region, IgG is slightly higher than IgM.

10. Conclusion

The intestinal epithelium can be stimulated by growth factors, cytokines, hormones, neuropeptides, polyamines, microorganisms etc. molecules. As a result of all these gene transcription and translation signals, survival, differentiation, proliferation, regeneration, apoptosis, regulation of actomyosin cytoskeleton, cell movement, migration, regulation of intercellular permeability and pro-inflammation or anti-inflammation are provided. With all these mechanisms, the effects of microbiota and environmental factors on immunity are observed. Especially with the 'gut homing' mechanism, dietary products or pathogens not only cause a reaction in the intestine, but also cause a reaction in the body area where the immune disorder like Defects of any adhesion molecule or signaling molecule, is present. when the intestine is directly encountered with the stimulus, the defective response will also affect the body region where the same defect is present and personal diseases will occur.

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