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Leukocyte–epithelial interactions

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As a 'double-edged sword', neutrophil (polymorphonuclear leukocyte) migration across epithelial-lined organs is an important component of host defense, but it also results in epithelial pathophysiology and disease symptoms. There have been significant advances in better understanding the mechanisms of how leukocytes cross the vascular endothelium to exit the bloodstream; however, many of the mechanisms that govern polymorphonuclear leukocyte transepithelial migration are different and we are only just beginning to understand them. Recent findings include new junctional adhesion molecules and carbohydrate moieties as receptors for migrating neutrophils. In addition, new insights into leukocyte–epithelial signaling events have emerged that are beginning to shed light on the role of SIRP–CD47 interactions in regulating the rate of neutrophil transepithelial migration and how neutrophils modulate epithelial barrier function.

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Abbreviations

AJC	apical junctional complex
CAR	coxsackie adenovirus receptor
ICAM	intercellular adhesion molecule
IgSF	immunoglubulin superfamily
ITIM	immunoreceptor tyrosine-based inhibitory motif
JAM	junctional adhesion molecule
MLC	myosin light chain
PMN	polymorphonuclear leukocyte
SIRP	signal regulatory protein
TJ	tight junction

Introduction

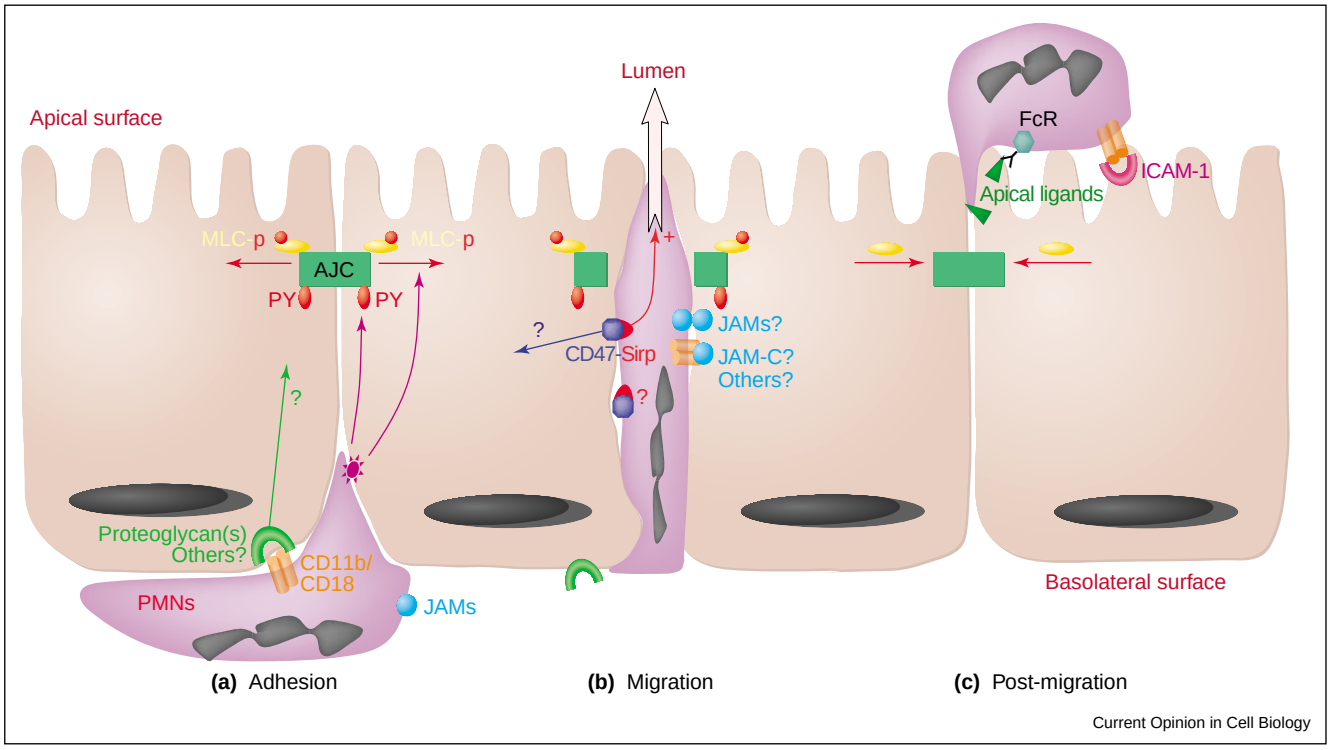
Leukocyte–epithelial interactions involve many fundamental cell processes, including, but not limited to, adhesion, migration, secretion, phagocytosis and apoptosis. In this review, we will focus primarily on current evidence that defines the mechanisms by which leukocytes (particularly polymorphonuclear leukocytes [PMNs]) use to migrate across epithelial surfaces in a polarized fashion from the basolateral to apical membrane (Figure 1).

PMN transepithelial migration can be viewed as a multistep process, with each stage governed by distinct mechanisms. The initial step consists of firm adhesion of PMN to the basolateral epithelial membrane and appears to be mediated exclusively by the leukocyte β_2 integrin CD11b/CD18 (also known as Mac-1, CR-3) [1]. This is distinct from PMN transendothelial migration in that both CD11b/CD18 and another β_2 integrin CD11a/CD18 (LFA-1) play significant roles in the latter. However, owing to marked differences in the microenvironments of these two cellular barriers, it is not surprising that there are significant differences in the adhesive interactions governing transendothelial and transepithelial migration. For example, selectins (e.g. CD62E, P- and L-) and CD31 (PECAM) [2], two important molecules involved in PMN interactions with vascular endothelium, do not appear to be involved in PMN transepithelial migration [3]. Although CD11b/CD18 plays a pivotal role in regulating PMN transepithelial migration, the precise nature of epithelial counter-receptor(s) remain elusive but are likely to include fucosylated proteoglycans and protein components of intercellular junctions.

In addition to cell–cell adhesive interactions, subsequent stages in the migration of PMNs across epithelia must involve signaling events that result in rapid opening and closing of tight junctions (TJs), to allow passage of cells and preservation of the epithelial barrier [4•]. Additional events subsequent to initial adhesion of PMN to epithelia involve CD47 (also known as integrin-associated protein [IAP]), an immunoglobulin superfamily (IgSF) member that has been shown to play a role in facilitating PMN transmigration [5,6]. Of the CD47-mediated signaling events that have been proposed to explain its role in regulating PMN migration, the identification of signal regulatory protein α (SIRPα) as a CD47-binding partner suggests that bidirectional signaling events after ligation of these proteins is important; however, we are only just beginning to understand the details of these signaling pathways and how they are related to CD47 function in regulating PMN transmigration. Events occurring late in the PMN transmigration response involve interactions of PMNs with the apical epithelial plasma membrane in the presence of the external environment. Here, PMN can adhere to apical ligands such as intercellular adhesion molecule 1 (ICAM-1), antigen-bound antibodies or pathogens, while eliciting functional responses from the epithelium that can aid in immune surveillance or result in epithelial injury.

Our current understanding of leukocyte interactions with epithelial cells can be summarized in a model detailed in Figure 1. As shown in this model, PMNs cross epithelia in

Figure 1



Leukocyte–epithelium interactions: model of neutrophil transepithelial migration. The process of PMN migration across an epithelium occurs in three sequential stages, highlighted as adhesion, migration and post-migration. **(a)** Initially, PMNs (purple) adhere to the basolateral membrane of the epithelial cell via CD11b/CD18 interactions with epithelial counter-receptors (green) that probably include multiple fucosylated proteoglycan(s), and other currently undefined ligands. Contact of PMNs with the epithelial basolateral surface results in phosphorylation (p, red circles) of the myosin light chain (MLC, yellow ovals) at the apical junction complex (AJC; comprising tight and adherens junctions) and tyrosine phosphorylation of TJ protein components (PYs; red ovals). These events serve to regulate opening and closing (red arrows) of the AJC and might facilitate subsequent migration of PMNs across the epithelium. **(b)** During the migration stage, interactions between epithelial CD47 (dark blue) with PMN SIRPα appear to enhance the rate of PMN transepithelial migration. However, since CD47 is also expressed on PMNs, *cis* interactions with PMN SIRPα are also possible. During transepithelial migration, adhesive interactions of PMNs with epithelial intercellular junction proteins are likely to occur. Candidate receptors include JAM-C and other TJ-associated IgSFs ('Others?'). In addition, heterophilic/homophilic interactions between JAM proteins that are expressed on both PMNs and epithelial cells might have dual roles in both regulating PMN migration and in forming a seal around migrating PMNs to maintain barrier function. **(c)** After migration across the AJC (post-migration), PMNs reach the lumen and contact the apical epithelial membrane. Here, apically expressed ICAM-1 would be accessible as a ligand for CD11b/CD18 and might serve as a foothold for PMNs on lumenal surface. In addition, as has been observed in some disease conditions associated with abundant PMN transmigration, auto-antibodies against apical ligands could mediate PMN adhesion and activation by binding to Fc receptors (FcRs).

a series of sequential molecular interactions at the level of the basolateral and apical epithelial membranes. In the sections below, we will focus on the molecular basis of PMN–epithelial-cell interactions, with emphasis on protein–protein interactions and cell–cell signaling events that are involved at each of these stages. Although epithelial cell responses to inflammatory mediators and pathogens have potent effects on interactions with leukocytes through release of numerous epithelial-derived factors, this is beyond the scope of this review and will not be discussed.

Adhesive receptors involved in leukocyte transepithelial migration

In vitro experiments using model epithelial cell monolayers have demonstrated conclusively that ~90% of PMN migration across intestinal epithelial monolayers can be blocked with monoclonal antibodies to the PMN β_2 integrin CD11b/CD18, and that leukocytes deficient in β_2 integrins fail to transmigrate. In addition, PMN adhesion to epithelial monolayers is blocked by anti-CD11b monoclonal antibodies, and epithelial cells bind specifically to purified CD11b/CD18. These observations indicate that CD11/CD18-mediated adhesion represents an early event in the transepithelial migration response (Figure 1). The ligand-binding properties of CD11b/CD18 have been well-described [7]. Function-mapping studies using domain-specific antibodies have demonstrated that the inserted domain (the I domain), a stretch of 200 amino acids of αM subunit, is a major binding domain for CD11b/CD18 ligands, including epithelial cells [8]. Numerous studies have shown that the αM I

domain is promiscuous in ligand binding, having several known receptors — including fibrinogen [9], ICAM-1 [10], elastase [11], heparin [12] and hookworm-derived PMN inhibitory inhibitor [13]. However, none of these ligands appear to mediate PMN adhesion during early stages of transepithelial migration. Recent studies have suggested that, in addition to the I domain, a lectin-like domain on CD11b might also play a role in ligand binding and cell adhesion [14].

Concerning epithelial ligands for CD11b/CD18, so far no basolaterally expressed epithelial ligand for CD11b/CD18 has been identified that modulates PMN transepithelial migration in the physiologically relevant basolateral→apical direction. Progress on identification and characterization of epithelial counter-receptor(s) has been relatively slow, most likely because of the presence of more than one epithelial receptor and the lack of appropriate reagents to screen for ligands. What is known is that epithelial receptors for CD11b/CD18 are sensitive to proteinase K [15] and that CD11b-mediated adhesion is upregulated under inflammatory conditions [15,16]. These observations support the existence of an epithelial protein receptor(s). Interestingly, trypsinized epithelial cells retain the ability to specifically bind to purified CD11b/CD18, suggesting that the epithelial ligand(s) for CD11b/CD18 are trypsin-insensitive [8]. ICAM-1 [10], the best-characterized cellular ligand for CD11b/CD18, is an attractive candidate epithelial receptor; however, ICAM-1 is normally not expressed on intestinal epithelia except during inflammatory conditions [17] or invasion by certain bacterial pathogens [18]. Furthermore, when ICAM-1 expression is induced in the intestine, it is upregulated on the apical rather than basolateral surface. Under these circumstances, it has been shown that ICAM-1 is physically not accessible as a ligand for migrating PMN [17]. However, things might be different in the airways, where epithelia can have a more flattened morphology and upregulation of ICAM-1 expression is localized at the apical region of cell boundaries [19]. Under these conditions, the migrating front of a PMN within the epithelial paracellular space might be able to bind to ICAM-1. Furthermore, ICAM-1 is strongly induced by viral infection of airway epithelial cells [20] in an NF-κB-dependent fashion, which, by analogy of the well-documented role of ICAM-1 in leukocyte–endothelial interactions, would support a role in leukocyte adhesive interactions. Thus, under organ-specific conditions, ICAM-1 might play a physiologically relevant role in PMN transepithelial migration, as suggested by others [19,21].

There is considerable evidence that CD11b/CD18 might bind to carbohydrate determinants on epithelial cells. Sulfated polysaccharides such as heparin and heparan sulfate have been shown to bind to CD11b/CD18 [12] and can block the initial adhesive stage of PMN transepithelial migration [3]. Despite this observation, the identification of candidate heparan sulfate proteoglycans functioning as epithelial ligands has not been reported. Syndecan-1 and -3 are good candidate heparan sulfate proteoglycans that are expressed abundantly on epithelial cells; however, these proteoglycans fail to inhibit epithelial cell binding to purified CD11b/CD18 (CA Parkos, unpublished). Recently, it was shown that fucoidin, a complex polysaccharide containing sulfated fucose, binds avidly to CD11b/CD18 and potently inhibits epithelial cell adhesion to the purified integrin [22•]. There is abundant expression of fucosylated neoproteoglycans on epithelial cells. Indeed, probing of western blots of fucosylated epithelial-cell proteins with purified CD11b/CD18 has revealed several candidate molecules that remain to be characterized [22•].

There are several additional candidate epithelial receptors for migrating leukocytes. Recently, many new epithelial IgSF proteins, including junctional adhesion molecules (JAMs), nectins, coxsackie adenovirus receptor (CAR) and related proteins, have been described that have roles in cell adhesion and migration. Because these adhesive molecules are mainly localized to the apical junctional complex (AJC), comprising the adherens and TJs, they are ideal candidate receptors for transmigrating PMNs. Interestingly, proteins from these families have been shown to function as receptors for different viruses and are required for viral entry into epithelial cells [23–25]. Of these proteins, the most abundant evidence for involvement in leukocyte adhesion/transmigration comes from studies on JAM family members (JAM-1, -2 and -3, recently re-designated as JAM-A, -B and -C, respectively). Studies on murine JAM-A by Dejana and co-workers [26,27] demonstrated expression at epithelial and endothelial intercellular junctions and that monoclonal antibodies against JAM-A inhibited monocyte and neutrophil transendothelial migration *in vitro* and *in vivo*. Subsequently, Ostermann *et al.* [28•] reported that JAM-A binds specifically to CD11a/CD18 and mediates T-cell attachment to endothelial cells. It was suggested that JAM-A might serve as a ligand for CD11a during PMN transendothelial migration [28•]; however, if JAM-A is involved in PMN transepithelial migration, the mechanism is unlikely to involve CD11a/CD18 because monoclonal antibodies against CD11a do not inhibit PMN transepithelial migration [1]. In studies on human JAM-A function, several JAM-A antibodies tested to date have failed to demonstrate inhibition of PMN or monocyte transendothelial/transepithelial migration [29,30]. A likely explanation for these differences is that the antibodies bind to different epitopes. Demonstration of direct binding interactions between purified JAM-A and purified CD11b/CD18 would help to resolve this question.

Other JAM-family members have been implicated as leukocyte receptors, including JAM-B and -C [31,32]. In a recent report by Santoso *et al.* [33••], platelets expressing

JAM-C were shown to bind to CD11b/CD18 on PMNs, an effect that was inhibited by anti-JAM-C antibodies. Furthermore, JAM-C purified from platelets binds to CD11b/CD18 *in vitro* [33••]. However, it remains to be shown whether JAM-C is expressed in epithelial cell and plays a role in regulating PMN migration across epithelia.

Post-adhesive events that regulate polymorphonuclear leukocyte transepithelial migration

As highlighted in Figure 1, subsequent to CD11b/CD18-mediated adhesion, PMNs rapidly migrate along the lateral epithelial membrane and must traverse the TJs before reaching the lumenal compartment. This process does not appear to involve proteolysis or oxidant production [34], it but clearly involves cell surface protein–protein interactions and cell signal transduction events. Studies suggest that an epithelium will rapidly open its TJs to allow passage of PMNs and that this is followed by rapid reassembly to maintain barrier function. Teleologically this makes sense, because under normal conditions, a major percentage of circulating PMNs end up in the colon via transepithelial migration. If rapid resealing did not occur after migration, the epithelial barrier would be seriously compromised. However, under conditions of high-density PMN transepithelial migration, such regulation would be lost, resulting in disruption of the barrier and enhanced permeability, as has been shown in many studies [35].

JAM proteins are good candidate molecules for regulating barrier function during PMN transepithelial migration, owing to their heterophilic/homophilic binding properties combined with dual expression at intercellular junctions on both epithelia and PMNs [32,36,37]. These properties might allow migrating PMNs to use JAMs for adhesion, as discussed above; or they might help to provide a transient seal around migrating cells for maintenance of barrier function. In support of this idea, Rescigno *et al.* [38] presented data suggesting that dendritic cells can selectively express TJ proteins during penetration of the intestinal epithelium to sample lumenal antigens, which might help to form a seal between the leukocyte and the epithelial cell. Although PMNs have not been shown to express the TJ proteins ZO-1, occludin or claudins, they express JAM proteins abundantly. Thus, one could envision potential adhesive interactions between JAM proteins not only facilitating transepithelial migration but also helping to maintain barrier function. This hypothesis is not inconsistent with observations from Luscinskas and co-workers [39], who report that endothelial JAM tagged with green fluorescent protein forms a transient ring around transmigrating PMNs.

Recently, it has been shown that when chemotactically driven PMNs contact the basolateral epithelial surface, there are rapid cell–cell signaling events that result in enhanced permeability. In particular, studies by Edens *et al.* [4•] demonstrated rapid and dramatic decreases in transepithelial resistance, paralleling enhanced paracellular permeability to small solutes that were dependent on a transepithelial gradient of chemoattractant and PMN contact with the basolateral epithelial membrane, but were independent of transepithelial migration. By avoiding artefactual degradation of epithelial intercellular junction proteins by PMN proteases, as has been well documented in the endothelial and epithelial literature [40,41], it was also shown that there was no gross morphological alteration in the amount or distribution of several intercellular junction proteins, despite enhanced permeability. In addition, this was a polarized epithelial response, since no disruption of barrier occurred in the absence of transepithelial migration when PMNs were stimulated to transmigrate in the reverse direction from the apical epithelial membrane. While speculative, such a response could serve to facilitate transepithelial migration in the physiologically relevant basolateral→apical direction.

Which epithelial intracellular events mediate such PMN-induced barrier disruption? As has been observed during PMN transendothelial migration [42], there is phosphorylation of the regulatory subunit of myosin light chain (MLC), resulting in contraction of the perijunctional actin–myosin ring and the separation of epithelial cells. Other signaling events also occur in the same timeframe that result in morphologically apparent tyrosine and serine phosphorylation. Although changes in phosphorylation of the TJ protein occludin would be an attractive regulatory mechanism, this has not been observed [4•]; however, occludin still remains an attractive candidate for regulation, since mutation of its amino-terminal cytoplasmic domain has been shown to alter PMN migration across epithelial cell monolayers [43]. Further studies are needed to define such protein targets.

On the PMN side of things, CD11b/CD18-dependent tyrosine-phosphorylation events have also been reported in neutrophils upon adhesion to endothelia [44]. These outside–in signaling events generated by β_2 integrin engagement trigger enhanced endothelial barrier function via MLC phosphorylation that have been attributed to release of the PMN primary granule constituent azurocidin [45]. It is not clear if similar events occur in epithelial cells, since no enhanced epithelial permeability was observed [4•] after supernatant transfers from activated PMNs. In aggregate, however, the above observations support adhesion of PMNs to the epithelial basolateral membrane, resulting in rapid activation of protein kinases that culminates in enhanced permeability. These events are highlighted in Figure 1.

CD47 regulation of polymorphonuclear leukocyte transepithelial migration

CD47, a multiple membrane-spanning IgSF member [46], has been shown to play a significant role in regulating

PMN transepithelial migration after initial β_2-integrin-dependent adhesion [6]. CD47 is universally expressed in all cells, and antibodies have been shown to potently inhibit PMN transmigration across matrix-coated filters and cell systems [5]. Numerous studies have indicated that CD47 has many other functions: in regulating integrin αvβ3 binding to vitronectin, as a receptor for thrombospondin-1, regulating red blood cell clearance, PMN phagocytosis, T-cell and dendritic cell activation, apoptosis and macrophage multinucleation (recently reviewed in detail by Brown and Frazier [47•]). Despite this wealth of data, the mechanism of how CD47 regulates PMN transepithelial migration is not known. *In vitro* and *in vivo* studies suggest that both PMN and epithelially expressed CD47 function to facilitate PMN transmigration [5,6,48]. This is dramatically illustrated in CD47-deficient mice, which rapidly succumb to *E. coli* sepsis owing to a delay in recruitment of PMNs to the site of infection [48].

Studies to dissect the mechanism of these CD47-dependent responses have been complicated by the fact that CD47 is expressed on both PMNs and the basolateral membrane of epithelial cells. It is clear that PMN-expressed CD47 plays a role in transmigration, because anti-CD47 monoclonal antibodies delay PMN migration across filters [5]. It is also clear that epithelially expressed CD47 plays a role in transmigration, because PMN migration across epithelial cell monolayers deficient in CD47 is significantly enhanced after stable transfection with CD47 [5]. Thus, epithelial CD47 interacts with PMNs in some way to enhance the migration response, whereas ligation of PMN CD47 by antibodies results in delayed transmigration.

These observations and many others suggest that CD47 functions as a signaling molecule. Indeed in other cell types, CD47 has been shown to couple with a heterotrimeric G protein [49]. Although this has not been shown in PMNs, G-protein-coupled downstream signaling intermediates such as cAMP have potent modulatory effects on PMN transmigration [50]. It is also possible that CD47 interacts with other integrins within the plane of the PMN plasma membrane in a *cis* fashion, to regulate integrin function, as has been described for αvβ3 [46,51]. An attractive integrin candidate for regulation by CD47 in PMN is CD11b/CD18, because of its important role in transepithelial migration. However, while CD11b/CD18 function has been shown to be modulated in a *cis* fashion by other proteins (such as the urokinase receptor [CD87]) [52], an association with CD47 has yet to be shown. There is also evidence of downstream tyrosine phosphorylation events in PMN mediated by CD47-binding to ligand [5]. In particular, inhibitory effects of anti-CD47 monoclonal antibodies on PMN migration across matrix-coated filters can be completely reversed by genestin, a tyrosine kinase inhibitor (PMN target unknown).

Concerning epithelial CD47 responses during transmigration, virtually nothing is known. Experiments examining the effect of CD47 monoclonal antibodies on epithelial barrier function have been inconclusive. Furthermore, anti-CD47 monoclonal antibodies do not modulate the transmigration-independent enhancement of permeability induced by PMNs [4•].

New insights into the mechanism of CD47 function in PMN transmigration came with the identification of SIRPα as a cellular receptor [53]. SIRPα is one of at least 15 SIRP members of a family of transmembrane glycoproteins that have a more limited expression pattern compared with CD47 but are heavily expressed in granulocytes, subsets of other leukocytes, central nervous system and endothelial cells. Structurally, SIRPα contains an amino-terminal extracellular domain that has three immunoglobulin-like loops, a single transmembrane domain and a carboxy-terminal intracellular domain that contains four tyrosine residues that form two immunoreceptor tyrosine-based inhibitory motifs (ITIMs). Similar to other ITIM-domain-containing proteins (for a review of ITIMs, see [54]), SIRPα has been implicated in both positive and negative regulation of cellular responses to a wide variety of different stimuli through ligand-induced interactions with tyrosine phosphatase-1 or 2 (SHP-1 and 2) [55]. Important insights into the role of SIRP–CD47 interactions came from the observation that SIRPα-expressing splenic macrophages actively phagocytose syngeneic red blood cells that don't express CD47 [56], suggesting that CD47 ligation of SIRPα serves to down-regulate a phagocytosis response.

Such SIRPα-mediated signaling could provide a mechanism for enhanced PMN transepithelial migration that has been observed after epithelial transfection with CD47 [5]. This hypothesis would suggest positive downstream signals from SIRPα ligation in the PMN by epithelially expressed CD47. Although this is a reasonable hypothesis, the mechanism is more complicated in that different results are obtained if SIRP is ligated by soluble receptor. Specifically, ligation of SIRP by a soluble form of the CD47 extracellular domain or SIRP-specific monoclonal antibodies results in an inhibition of transmigration [57•]. Furthermore, the kinetics of inhibition are distinct from those observed after ligation of CD47 by anti-CD47 monoclonal antibodies [57•]. Thus, CD47–SIRPα interactions appear to result in bidirectional signaling pathways with different functional consequences, depending on how the ligand is presented. This does not appear to be specific for transepithelial migration because similar findings have been reported for PMN transendothelial migration [58]. To further complicate things, both CD47 and SIRPα are co-expressed on the PMN cell surface, thus raising the possibility of other types of interactions, including those between adjacent PMN (*trans*), or ones within the plane of the PMN plasma membrane (*cis*).

Indeed, such interactions have been proposed to play a role in a CD47–SIRPα-mediated multinucleation response in macrophages [59]. The interactions of CD47 and SIRPα during PMN transepithelial migration are highlighted in Figure 1.

Late events in transepithelial migration: polymorphonuclear leukocyte interactions with the apical epithelial surface

After traversing the epithelial TJ, migrating PMNs reach the apical epithelial plasma membrane, where there are several functional consequences. Perhaps most importantly, PMNs can act to destroy lumenal pathogens. In doing so, activation of the NADPH oxidase and release of granule constituents not only aids in pathogen clearance but also has pathophysiological consequences. Tissue damage is a well-known consequence of PMN activation that is very prevalent in several mucosal diseases characterized by abundant PMN transepithelial migration. One physiological consequence of apical PMN activation is epithelial chloride secretion, resulting in fluid movement into the lumen and 'flushing' of the offending agent(s) out of the organ. Madara and co-workers [60,61] demonstrated that 5′-AMP released by PMNs into the lumen is converted to adenosine by CD73, followed by stimulation of lumenal chloride secretion through interaction with apically expressed adenosine A2b receptors.

How are PMNs retained at the apical epithelial surface, as observed in many inflammatory conditions? There is evidence that under certain pathophysiological conditions, deposition of immunoglobulin on the apical epithelial surface might serve to promote retention and activation of transmigrated PMNs. For example, many patients with ulcerative colitis and abundant PMN transepithelial migration have auto-antibodies against intestinal epithelial cells that decorate the apical epithelial membrane along with complement products [62]. Indeed, there is a report of an IgG1 antibody against an apical epithelial antigen that retains PMNs at the apical surface via Fc-mediated adhesion and is antigen-specific [63]. There are also leukocyte receptors such as ICAM-1 on the apical surface that are markedly upregulated under inflammatory conditions and after microbial infection. Under these conditions, ICAM-1 might serve as a foothold for PMNs and macrophages on the lumenal surface, serving to retain them at sites of inflammation. This mechanism would be particularly important in the face of shear force generated by air or fluid flow.

Conclusions

In this review, we highlight the current understanding of PMN adhesion and regulation of migration across epithelia. PMN transepithelial migration is a multistep process that is polarized and involves both adhesive interactions and cell–cell signaling events. CD11b/CD18-mediated adhesion to the epithelial basolateral membrane most likely involves multiple epithelial ligands. Although specific epithelial adhesive counter-receptors for migrating PMNs have not been identified, candidates include fucosylated neoproteoglycans and a growing list of intercellular junction proteins that might also serve to preserve transiently the epithelial barrier as PMNs transmigrate. Cell signaling events, including phosphorylation of epithelial intercellular junction proteins and the regulatory subunit of MLC, are likely to facilitate regulated opening and closing of intercellular junctions, whereas bidirectional signaling events mediated by binding interactions between SIRPα and CD47 fine tune the rate of PMN migration across epithelia. Evidence suggests that late events in PMN transepithelial migration can involve adhesive interactions with apically expressed receptors such as ICAM-1 or bound immunoglobulin in addition to PMN-elicited functional responses that can either promote mucosal cleansing or result in epithelial damage.

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- • of special interest
- •• of outstanding interest

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