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Review

Polymeric immunoglobulin receptor

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Abstract: The surface of mucosal sites, such as the intestinal tract, are covered by epithelial cells. To protect the intestinal environment from invading pathogens and maintain homeostasis, the human body developed an exquisite acquired immune system, referred to as the mucosal immune system, in which epithelial cells and lymphocytes function cooperatively. The main player in this immune system is the polymeric immunoglobulins (pIgs), in particular dimeric IgA (dIgA). To exert its protective effect, dIgA produced in the lamina propria must be transported to the intestinal lumen across epithelial cells. This process is called transcytosis and is mediated by polymeric immunoglobulin receptor (pIgR), which is exclusively produced by intestinal epithelial cells (IECs). DIgA is captured by pIgR on the basolateral surface of IECs and transcytosed to the opposite side of IECs. The dIgA-pIgR complex is expressed on the apical surface of IECs and proteolytically cleaved to generate secretory IgA (SIgA). This review describes the current understanding and recent progress in this research field. (J Oral Sci 53, 147-156, 2011)

Keywords: dimeric IgA; polymeric immunoglobulin receptor; intestinal epithelial cells; transcytosis.

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Introduction

The surfaces of mucosal sites such as the gastrointestinal and genitourinary tracts are continuously bombarded by various stimuli. To protect mucosal sites from these stimuli, innate and adaptive immunities must function cooperatively (1-4). The surfaces of mucosal sites are covered by epithelial cells, such as the intestinal epithelial cells (IECs). IECs play a pivotal role in maintaining intestinal homeostasis (1,5,6) by forming a physical barrier and by driving innate and adaptive immunity against invading pathogens. The most important adaptive immune system in mucosal sites is the mucosal immune system, and the main player in this system is the polymeric immunoglobulins (pIgs) (7,8), which are produced by antibody-secreting plasma cells that accumulate in the lamina propria. In order to exert a protective function, pIgs are transported to the luminal side, across IECs, and released into the intestinal lumen. This process is called transcytosis and is mediated by the transmembrane glycoprotein, polymeric immunoglobulin receptor (pIgR) (9). The present review will discuss the functional importance of pIgR.

Overview of the sIgA System

The surface of the intestinal tract is covered by IECs, which are columnar cells that have a luminar surface with numerous tightly packed microvilli. Adjacent IECs are connected by junctional complexes (10). Among these, tight junctions form belt-like structures that encircle the apical end of IECs and separate the surface of IECs into apical and basolateral surfaces (Fig. 1). The protein composition of the membranes of these surfaces differs greatly, and tight junctions prevent lateral diffusion of membrane proteins between the apical and basolateral surfaces. The IECs are separated from underlying connective tissue, ie, the lamina

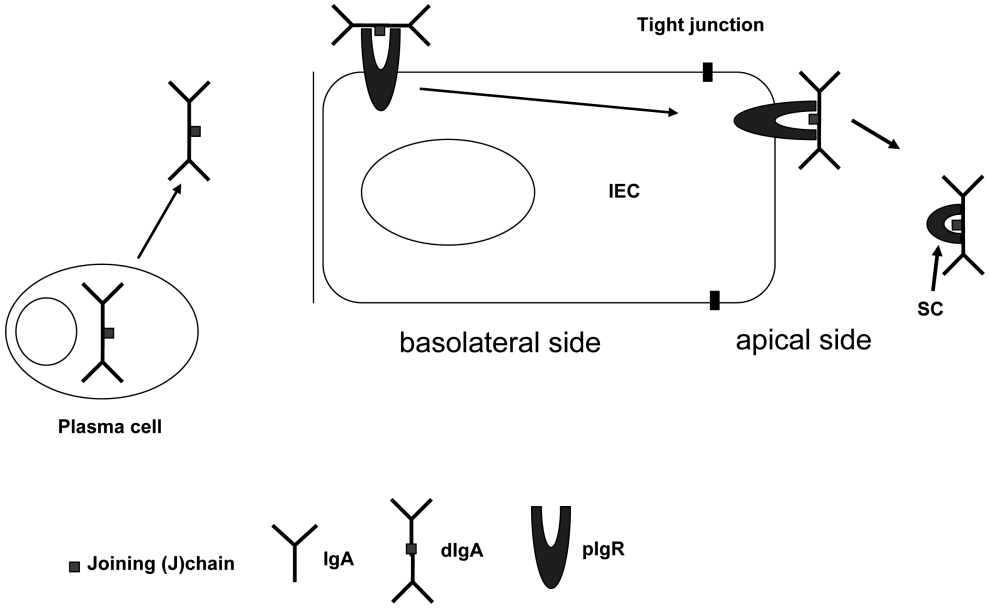

Fig. 1 Transcytosis of dIgA.
The J-chain containing dIgA is produced and secreted by plasma cells accumulated in the lamina propria. Secreted dIgA is captured by pIgR expressed in IECs at the basolateral cell surface. The dIgA-pIgR complex is internalized and transcytosed to the apical plasma membrane, and the extracellular portion of pIgR is proteolytically cleaved and released to the lumen with dIgA.

propria, by the basal lamina. The lamina propria is composed of various cell types, including fibroblasts and smooth muscle cells; however, the most striking feature of the lamina propria is the infiltration of plasma cells that secrete IgA isotype (9). The greatest accumulation of IgA-secreting plasma cells is in the crypt area. Moreover, most IgA-secreting plasma cells secrete the dimeric form of IgA, dimeric IgA (dIgA). Detailed investigation of the structure of dIgA has revealed the existence of the joining chain (J-chain) (11-14), a 15-kDa acidic protein that contributes to the dimerization of IgA (15). The J-chain is critically important in the binding of dIgA to its receptor, pIgR (16-19). The biological function of dIgA is neutralization of harmful antigens in the luminal side of the gut. To exert its protective effects, however, dIgA must be transported across the IECs and secreted in the lumen. This transport pathway – transcytosis – is mediated by pIgR (9). DIgA secreted in the lamina propria is captured by pIgR at the basolateral surface, internalized by IECs, and transported to the apical surface. The transported dIgA-pIgR complex is expressed on the apical surface of IECs and released by proteolytic cleavage. Consequently, the released dIgA, secretory IgA (SIgA), is composed of extracellular pIgR and dIgA.

The *pIgR* Gene

The human *pIgR* gene is encoded by a single copy gene and is localized in the q31-q41 region of chromosome 1 (20,21). The entire *pIgR* gene contains 11 exons spanning 18 kb (22). As illustrated in Fig. 2, the first intron is the longest and is localized between exons 1 and 2. The initiation codon and the leader peptide is encoded by exon 2. The relationships between exon structures and their responsible domains are also shown in Fig. 2. The *pIgR* gene was first cloned in rabbit (23), and a comparison of rabbit pIgR mRNA with human pIgR mRNA revealed that domains 2 and 3 are sometimes deleted in rabbit by alternative splicing (24,25). Domain 6, transmembrane, and cytoplasmic portions are encoded by exons 7 to 11. Database analysis has identified single-nucleotide polymorphisms (SNPs) in the human *pIgR* gene, some of which were reported to be associated with increased risk for nasopharyngeal cancer and IgA nephropathy (26,27).

The Structure of pIgR

The pIgR is a type I transmembrane protein with a molecular weight of approximately 120 kDa (Fig. 3). The extracellular, transmembrane, and cytoplasmic portions of pIgR are composed of 620, 23, and 103 amino acids,

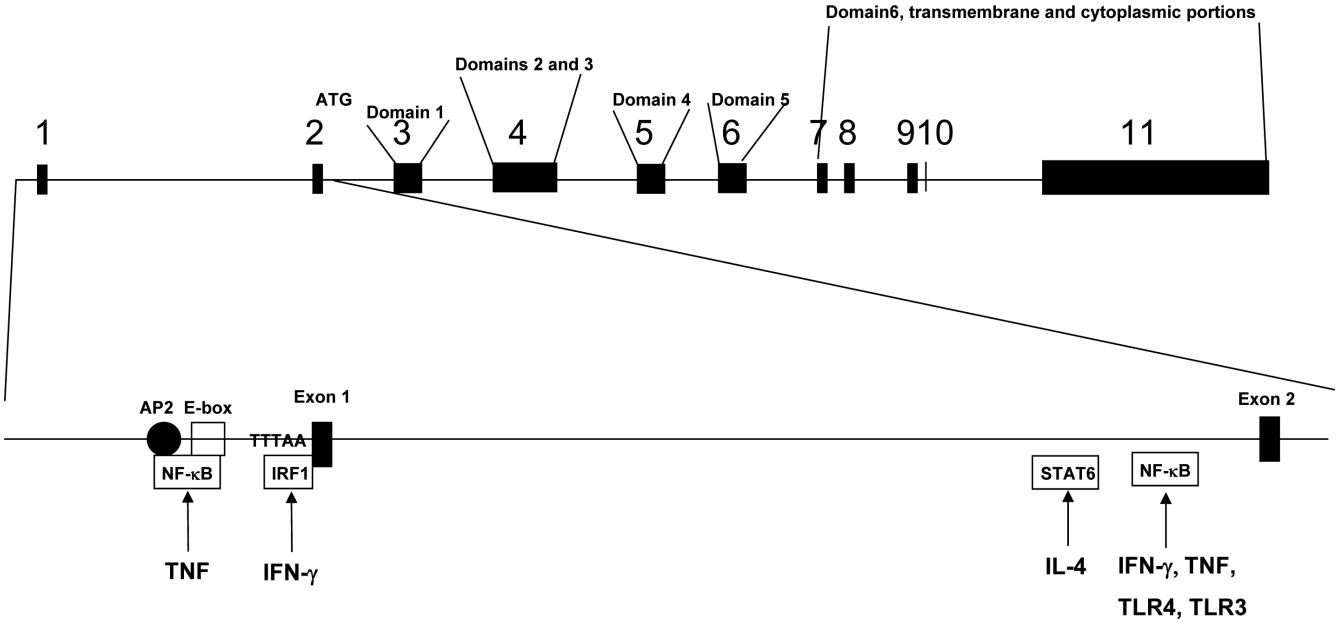

Fig. 2 Exon-intron organization of human pIgR.
The human *pIgR* gene is composed of 11 exons. The longest intron is the first, localized between exons 1 and 2. The relationships between exons and their coding domain are shown. The 5'-flanking region and intron 1 contain several transcription factor-binding sites. Each transcription factor is responsible for the signaling of the indicated cytokines.

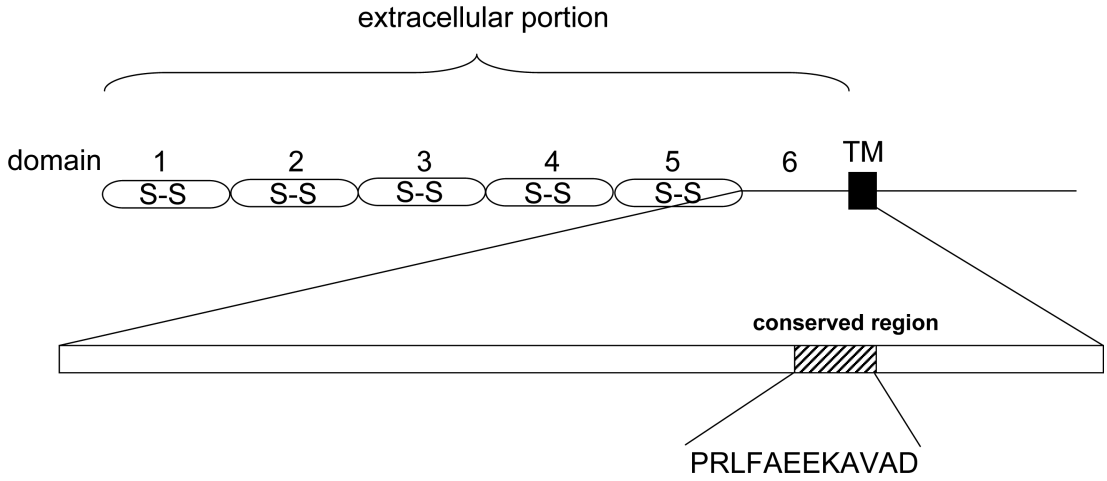

Fig. 3 Structure of human pIgR.
The extracellular portion of human pIgR is composed of 6 domains. N-terminal 5 domains are immunoglobulin-like domains, and each domain contains an intradomain disulfide bond. The sixth domain is the most divergent. The hatched region shows amino acids that are highly conserved between several species and is believed to be the cleavage signal. Human pIgR is a type I transmembrane protein and has a relatively long intracellular portion.

respectively (23). The extracellular portion of pIgR is composed of five immunoglobulin homologous domains (domains 1 to 5) and one non-homologous domain (domain 6). Immunoglobulin homologous domains contain internal disulfide bonds. Alignment of the pIgR amino acid sequences revealed that cysteine residues of these disulfide bonds are completely conserved in several species (28). Domain 1 is thought to be the most important domain for the binding with dIgA (29,30), and the amino acid sequence is the most highly conserved. Domain 6 is closest to the

transmembrane portion, and the amino acid sequence is highly variable among species as compared with the other immunoglobulin homologous domains. This domain contains a possible proteolytic cleavage site. The PIgR molecule has a relatively long intracellular portion. Using the Madin-Darby canine kidney (MDCK) cell system, this portion was revealed to have highly conserved signals for intracellular sorting, endocytosis, and transcytosis (31).

Transcriptional Regulation of the *pIgR* Gene

As illustrated in Fig. 2, the 5'-regulatory region, exon 1, and intron 1 contain many transcription factor-binding sites (32-35). The transcription initiation site is localized in exon 1, and the pIgR promoter TTTAA sequence is localized approximately 30 bp upstream from that site. Mutational analysis revealed that the E-box motif is localized 71 bp upstream of the transcription initiation site and that this motif is essential for basal promoter activity. The E-box motif ($CAC^{G}/_{A}TG$) is the binding site for the basic helix-loop-helix/leucine zipper family protein. The activator protein-2 (AP2) site was reported to be localized adjacent to this motif (34).

Regulatory factors in pIgR expression

The pIgR is produced solely by IECs, and they localize to interact with many different cells and microorganisms; thus, regulation of pIgR expression is extraordinarily complex. The key regulator of pIgR expression is pro-inflammatory cytokines, such as interferon-γ (INF-γ) (36,37), tumor necrosis factor (TNF) (38), and interleukin-1 (IL-1) (39). All these cytokines were reported to upregulate expression of pIgR mRNA in HT-29, a human colon adenocarcinoma cell line. The Th2 cytokine, IL-4, was also reported to synergistically enhance expression of pIgR in combination with INF-γ (40-43).

IFN-γ

The IFN family comprises type I, type II, and type III IFN (44,45). IFN-γ belongs to type II IFN and is mainly produced by T helper 1 (Th1) cells. Each IFN exerts its effect through specific receptors. The receptor for IFN-γ is composed of a heterodimer of IFN-γ receptors 1 and 2 (IFNγR1 and IFNγR2). The IFN-γ-binding signal is transduced by the Janus kinase (JAK)/signal transducer and activates the transcription 1 (STAT1) pathway (44,45). Treatment of HT-29 cells with IFN-γ induces nuclear STAT1 and increases transcription of interferon regulatory factor 1 (IRF1) (46). Thus, induced IRF1 is thought to upregulate expression of pIgR mRNA. Although these observations indicate that the pIgR-enhancing effect of IFN-γ is indirect, IFN-γ stimulation also directly activates NF-κB to some extent. IFN-γ induces expression of pIgR through the IRF1 pathway in combination with the NF-κB pathway. A striking feature of IFN-γ is the cooperative enhancement of pIgR with IL-4 (40-43), which is a Th2 cytokine usually repressed by IFN-γ. However, in pIgR expression, both factors work synergistically to induce pIgR expression. The discovery that intron 1 of the *pIgR* gene contains a STAT6-binding site – an intrinsic transcription factor for the IL-4 signaling – shed light on the mechanisms underlying the cooperative effects of IL-4 and IFN-γ.

TNF

Downstream signaling of TNF is mediated by classical NF-κB, which has five subunits – p65, p50, p52, Rel-B, and c-Rel. Classical NF-κB is the heterodimer of p65 and p50 (47). In resting state, p65/p50 is localized in cytoplasm with the inhibitory protein IκB. When the cells are activated, IκB is rapidly phosphorylated by the IKK kinase complex (48). The phosphorylation of IκB rapidly liberates p65/p50, which translocates to the nucleus and induces transcription of their target genes. Each 5'-flanking region and intron 1 of the *pIgR* gene contains one NF-κB-binding site. These sites seem to function separately in inducing expression of pIgR by TNF stimulation, ie, they do not appear to cooperate. TNF-induced transcriptional activation of pIgR is relatively slow, and it has been reported that de novo synthesis of p50 is necessary for the induction of TNF-mediated pIgR expression (49).

Toll-like receptors (TLRs)

Conserved pathogen-associated molecular patterns (PAMPs) and host pattern-recognition receptors (PRRs), such as toll-like receptors (TLRs), retinoic acid-inducible gene I-like receptors (RLRs), and NOD-like receptors (NLRs), play crucial roles in inducing host innate immune responses (50,51). IECs have been shown to express various TLRs. Expression of TLRs is reported to be altered in certain disease states (52,53). Among TLR ligands, bacterial lipopolysaccharide (LPS) and double-stranded RNA (dsRNA), a replication byproduct of RNA virus, induced expression of pIgR mRNA via the NF-κB-binding site in intron 1 (54). Downstream signaling of TLR3 is distinct from other TLRs, which utilize the adaptor molecule MyD88. TLR3 signaling is instead mediated by TIR-domain-containing adaptor-inducing IFN-beta (TRIF). TLR3 signaling is activated by four pathways – NF-κB, IRF3, JNK, and p38 (55). In the induction of pIgR, binding of dsRNA to TLR3 has been shown to activate the NF-κB pathway; however, direct activation of the other

pathways has not been demonstrated (54). Interestingly, stimulation of HT-29 cells with dsRNA resulted in enhanced production of IRF1 (54). Although the regulatory region of the *pIgR* gene contains an IRF-binding site, the contribution of IRF1 to upregulation of pIgR mRNA is unknown. Furthermore, dsRNA-induced production of TNF was shown to induce pIgR production, and neutralization of TNF by its specific antibody diminished enhanced production of pIgR. The proinflammatory cytokines, including TNF and IFN-γ, induce expression of pIgR mRNA, and expression of IRF1 was correlated with pIgR mRNA level (54). The relationship between enhanced production of IRF1 and TNF due to dsRNA stimulation requires further study.

Biological Functions of pIgR

In addition to its receptor function, pIgR has other unique functions. The pIgR is transcytosed in IECs to either ligand (dIgA)-bound or -unbound forms. Both forms are proteolytically cleaved at the apical plasma membrane, which results in the release of secretory IgA (S-IgA) or free secretory component (fSC), respectively (9). The extracellular portion of pIgR bound to dIgA is called the secretory component (SC) and protects S-IgA from proteolytic degradation. SC is novel in that it is responsible for intracellular neutralization of some viruses (56-58). It is believed that dIgA internalized in IECs through pIgR encounters viral replication intermediates in endosomal compartments and eventually neutralize these antigens. However, the underlying mechanisms of this process remain to be elucidated.

PIgR also binds to bacterial components such as *Streptococcus pneumonia*-derived SpsA protein (59,60). FSC can bind to SpsA and prevent invasion of respiratory epithelial cells by *S. pneumonia*.

Intracellular Traffic of pIgR

MDCK cell system

The unique characteristics of intracellular traffic of pIgR were elucidated by using an elegant *in vitro* MDCK cell system (61,62). This experimental system utilized permeable membrane support to polarize MDCK cells transfected with pIgR cDNA. Transfected MDCK cells were successfully grown on the membrane, resulting in the formation of circumferential tight junctions. This structure divides the plasma membrane into apical and basolateral domains and allows pIgR to behave as it does *in vivo* (Fig. 4).

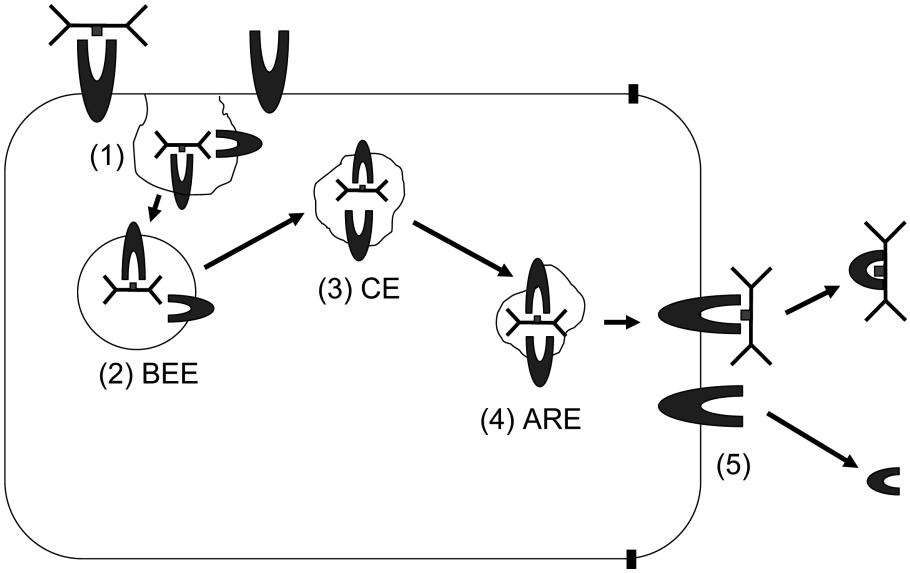

Fig.4 Steps in transcytosis.
The first step of transcytosis is internalization of the dIgA-pIgR complex by the clathrin-coated pit. PIgR is internalized even in the absence of its ligand (1). The internalized molecules are delivered to basolateral early endosomes (BEE) (2) and then to common endosomes (CE) (3), where the complex is segregated from other internalized molecules. The molecules are transported to the apical recycling endosomes (ARE) localized beneath the apical plasma membrane (4). The dIgA-pIgR complex or pIgR is expressed on the surface of the apical plasma membrane and proteolytically cleaved to generate S-IgA or SC (5).

Basolateral sorting

Most membrane proteins are glycoproteins, which are synthesized in the endoplasmic reticulum (ER) and transported to the Golgi apparatus to be modified by sugar moieties. PIgR is a highly glycosylated protein, and the modification process can be traced by a pulse-chase experiment (63). After the proteins pass through the trans-Golgi network (TGN), they are delivered to their final destinations by vesicle carriers. In the MDCK cell system, most pIgR was delivered to the basolateral side of the cells. Numerous experiments with a series of deletion mutants revealed that pIgR has the basolateral sorting signal in its cytoplasmic portion (64-66). This signal was composed of 17 amino acid residues and was located in the most proximal part of the cytoplasmic tail (64-66). This signal has been identified in other basolateral targeting proteins, and inactivation of this signal resulted in the proteins being wrongly delivered to the apical domain. These observations confirm the existence of an active basolateral targeting signal.

We generated a deletion mutant that lacks the entire cytoplasmic region of pIgR (ΔCL mutant) (67) (Fig. 5). This mutant was transfected to baby hamster kidney (BHK) cells by using a recombinant vaccinia virus-mediated transfection method (68), and the secretion of fSC was compared with that of wild-type pIgR. Most newly synthesized ΔCL mutant was secreted in the culture media, and no mutant pIgR was detected in the cell lysates (67). Our results further suggest that the cytoplasmic deletion mutant of pIgR was released from the cells immediately after its synthesis and that the cytoplasmic portion of pIgR has a plasma membrane retention signal (67).

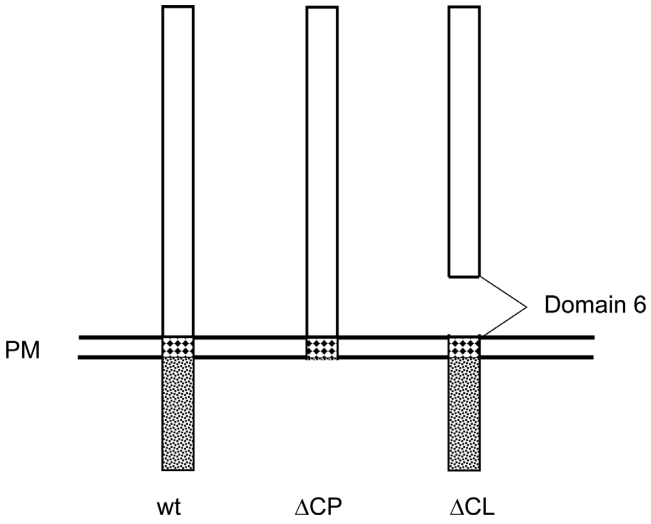

Fig. 5 The structures of deletion mutants.
Wild-type pIgR (wt) is a type I membrane protein comprising extracellular, transmembrane, and cytoplasmic portions. We generated whole cytoplasmic-deletion (ΔCP) and whole domain 6 deletion (ΔCL) mutants.
PM, plasma membrane

PIgR transcytosis

After reaching the basolateral surface, pIgR must be delivered to the apical plasma membrane. This targeting route is called transcytosis and is composed of several distinct steps. The first step is internalization, which occurs in the clathrin-coated pit on the basolateral plasma membrane (69). Three serine residues – Ser668, Ser726, and Ser734 – are important in this step (65). Internalized pIgR is delivered to the basolateral early endosomes (BEE) (step 2) and then to common endosomes (CE) (step 3) (70-72). The latter process is microtubule-dependent, and delivery is inhibited by incubating the cells with inhibitors (73). From both BEE and CE, pIgR can recycle back to the basolateral plasma membrane and be reused for the next round of transport. However, most pIgR are transported to the apical recycling endosomes (ARE) (step 4), which are localized just beneath the apical plasma membrane (74), and finally expressed on the apical surface (step 5).

pIgR cleavage

After reaching the apical plasma membrane, pIgR must be cleaved by a proteolytic enzyme to generate free secretory component (fSC) or sIgA. Using a rat hepatocyte system, the molecular mass of SC bound to pIgA was revealed to be decreased (75). Furthermore, fSC release was observed in the absence of pIgA, indicating that pIgA is not necessary for pIgR cleavage (76). These results reflect the fact that cleavage of pIgR to SC likely occurs near the transmembrane portion. Although several investigators have attempted to determine the C-terminal amino acid residue of fSC using the colostrum, the C-terminal end varied among preparations, and no consensus on the residue has emerged (77,78). Moreover, the absence of fSC in intracellular membranes suggests that pIgR cleavage occurs on the cell surface, not inside cells. Taken together, these results indicate that pIgR cleavage is a highly localized process. Although the enzyme responsible for pIgR cleavage has not been identified, its properties can be inferred by the findings of proteinase inhibitor experiments (74). Incubation of cells with leupeptin, a serine proteinase inhibitor, significantly inhibited release of fSC, which suggests that the pIgR cleaving enzyme is a serine proteinase. Another feature of pIgR cleavage is that it is not cell-type specific, because pIgR expressed in non-epithelial cells, such as fibroblasts, can be successfully

cleaved and released (67). We transfected BHK cells with pIgR cDNA, and expression of pIgR was confirmed by Western blotting and pulse-chase experiments (67). Using this expression system, we attempted to express a deletion mutant lacking domain 6 of the extracellular portion (Fig. 5, ΔCL mutant) and observed that fSC release was drastically inhibited. These results indicate that domain 6 of pIgR has an intrinsic signal for the pIgR to be recognized and cleaved by proteolytic enzyme (67). The 12 amino acids spanning from Pro589 to Asp600 are highly conserved in several species and are the putative cleavage site of pIgR (31). Based on this assumption, we constructed a deletion mutant lacking these 12 amino acids and transfected it to BHK cells. The efficiency of fSC release was reduced to approximately 60-70% of that of wild-type pIgR; however, the fSC level was significantly higher than that of the domain 6-deleted mutant (personal communication), which indicates that this conserved motif might have other functions than pIgR cleavage.

Concluding Remarks

During the last decade, enormous progress has been made in mucosal immunology. Mucosal surfaces, especially those of the intestinal tract, are always abundantly colonized with commensal bacteria. Since the discovery of the PRRs, the mechanism by which the host recognizes micro-organisms and maintains healthy states has been investigated by many researchers worldwide. In addition to adaptive immunity, the innate immune system has been shown to play a critical role in maintaining homeostasis at mucosal sites. Despite substantial progress, the proteolytic enzymes responsible for cleaving the extracellular portion of pIgR have not been elucidated. We are now constructing a variety of domain 6-truncation mutants of pIgR in an attempt to learn more regarding amino acids that are indispensable in pIgR cleavage. We hope that this approach will lead to detection of the intrinsically important cleavage signal of pIgR.

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