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Lung mucosal immunity: immunoglobulin-A revisited

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Lung mucosal immunity: immunoglobulin-A revisited. C. Pilette, Y. Ouadrhiri, V. Godding, J-P. Vaerman, Y. Sibille. ©ERS Journals Ltd 2001.
ABSTRACT: Mucosal defence mechanisms are critical in preventing colonization of the respiratory tract by pathogens and penetration of antigens through the epithelial barrier. Recent research has now illustrated the active contribution of the respiratory epithelium to the exclusion of microbes and particles, but also to the control of the inflammatory and immune responses in the airways and in the alveoli. Epithelial cells also mediate the active transport of polymeric immunoglobulin-A from the lamina propria to the airway lumen through the polymeric immunoglobulin receptor. The role of IgA in the defence of mucosal surfaces has now expanded from a limited role of scavenger of exogenous material to a broader protective function with potential applications in immunotherapy. In addition, the recent identification of receptors for IgA on the surface of blood leukocytes and alveolar macrophages provides an additional mechanism of interaction between the cellular and humoral immune systems at the level of the respiratory tract.
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Each breath carries in the inhaled air thousands of micro-organisms and microparticles into the respiratory tract. This exposure appears well tolerated by the host, which rarely reacts to this continuous stimulation. Thus, in normal conditions, the respiratory tract appears to be well equipped to efficiently eliminate exogenous material without generating a major inflammatory or immune response. The defence of the respiratory tract against pathogens relies on two distinct mechanisms, located in the airways (upper and lower) and the alveolar space, respectively. In the airways, mechanical defence appears to predominate and includes the deposition on the nasal and oropharyngeal surfaces and elimination through cough, sneezing, and mucociliary clearance. In contrast, the alveolar epithelium lacks mucociliary properties and therefore relies mostly on the alveolar macrophages to remove particles and micro-organisms reaching the alveolar space [1]. In addition, the respiratory tract can also call on several protective mechanisms whenever required (table 1). For example, the contribution of polymorphonuclear neutrophils (PMNs) to the defence of the lung against bacterial infection is well recognized [2], and recent research has elucidated important mechanisms of recruitment and activation of PMNs at sites of infection. Another area of research where major progress has been made concerns the epithelial cells. Thus, the bronchial epithelial cell which has long been recognized as a key element of the mucociliary system is now also considered as a pivotal cell in the control of inflammatory and immune responses against pathogens and biotoxics. The respiratory epithelium is able to initiate and perpetuate an inflammatory reaction in response to a variety of stimuli. In particular, bronchial epithelial cells produce interleukin (IL)-5, IL-8, regulated on activation, normal T-cell expressed and secreted (RANTES), and growth factors such as granulocyte macrophage-colony stimulating factor (GM-CSF), all implicated in attraction and/or activation of inflammatory cells [3]. Interestingly, IL-8, the most potent neutrophil chemoattractant, is released by bronchial epithelial cells in response to bacterial products [4]. In addition, the epithelium can probably participate in the immune response at an early stage after antigen deposition. This participation can occur since epithelial cells are recognized as antigen-presenting cells, both in the respiratory and digestive mucosa. Also, while it is well accepted that inflammatory mediators such as oxidants and proteases can damage the airways, conversely, it is likely that remodelling of the bronchial structures (as observed

Table 1. – Defence mechanisms of the respiratory tract

Upper respiratory tract (nose, oropharynx, larynx)
Mechanical
Nasal hairs and sneezing
Nasal, oropharyngal and sinusal ciliated epithelium
Saliva, mucus
Vocal cords
Innate immunity
Complement
Proteases
Lactoferrin
Acquired humoral immunity
Secretory immunoglobulin (Ig-A and IgM
Lower respiratory tract (tracheobronchial tree)
Mechanical
Mucociliary clearance
Cough and impaction on bronchial branching
Acquired cellular immunity
Bronchial-associated lymphoid tissue (BALT)
Humoral immunity
Secretory IgA and IgM
Lung parenchyma (alveoli and lung interstitium)
Surfactant products (SP-A, SP-B, SP-D)
Phagocytic cellular mechanisms
Resident alveolar macrophages
Phagocytosis
Oxygen and nitrogen metabolites
Lysozyme, acid hydrolases
Recruited polymorphonuclear neutrophils (from pulmonary microvessels)
Phagocytosis
Oxygen and nitrogen metabolites
Lactoferrin, defensins (human neutrophil peptides 1–4)
Bacterial/permeability increasing protein
Cationic antimicrobial protein (CAP/azurocidin)

in chronic disorders such as asthma, chronic bronchitis or cystic fibrosis) could modify the response of the host against inhaled pathogens and toxins.

Although lymphocytes are scarce in the normal airway and alveolar lumen, they are detected in the submucosa of the bronchi and when they are abundant, such as in some pathologies, they are sometimes organized in lymphoid tissue called bronchus-associated lymphoid tissue (BALT). A part of their role is related to the mucosal humoral immune response and more specifically to the production of immunoglobulin (Ig)-A. The defence mechanisms of the bronchial tree and lung parenchyma against infection, often associated with an inflammatory or immune response, have been the topic of extensive reviews and of several workshops [5]. However, the most recent information on the role of the mucosal humoral immune system (namely the secretory IgA system) has rarely been addressed in the literature devoted to the lung. Therefore, the present review will focus on the secretory IgA system, considering both the properties shared with other mucosa and those more specific to the respiratory tract. This appears to be of great importance when considering that IgA, the most abundant Ig in the mucosal fluids, can also interact with phagocytic cells. The first part will discuss the different steps and mechanisms of IgA production, transport, and activity, while a second part will consider more specifically the functions of IgA in mucosal tissues. The last part will be devoted to the putative roles of the mucosal IgA system in respiratory disorders, both considering pathophysiological aspects and potential therapeutical interventions.

Organization of the mucosal immunoglobulin-A system

Immunoglobulin-A structure and distribution

IgA [6] not only represents the predominant Ig in secretions, but has unique characteristics notably due to its association with a "transport piece" [7]. IgA is much less abundant in serum than IgG, but its catabolism is four-eight-fold faster (considering, respectively, monomeric and polymeric IgA). Thus, homeostasis of serum IgA requires a synthesis rate quite similar to that of IgG (21 $mg \cdot kg^{-1} \cdot day^{-1}$ for IgA *versus* 30 $mg \cdot kg^{-1} \cdot day^{-1}$ for IgG). By contrast, in the various mucosa and exocrine glands, IgA production is much higher than IgG and, considering both vascular and mucosal compartments, the daily IgA production appears thus quantitatively much more important than its IgG counterpart [8]. The secretory Ig system is characterized by a close cooperation between the mucosal lymphoid tissue, which assumes a continuous and adaptive production of Ig (mainly polymeric IgA) and the epithelium, which allows the transport of polymeric Ig (pIg) within the mucosal lumen through the polymeric Ig receptor (pIgR) [9]. Thus, the majority of polymeric IgA (pIgA) and IgM (pIgM) produced at these sites is transported across epithelia into the luminal environment, where secretory Ig is thought to inhibit adherence of noxious micro-organisms and antigens to the epithelium, performing a so-called "immune exclusion". Similarly, innocuous antigens seem ignored by the immune system through unclear mechanisms related to a "mucosal tolerance". These mechanisms provide an efficient "first-line" of defence of the 400 m^2 surface area of mucosa (100 m^2 for the lung, excluding the bronchial tree), preventing the development of a potentially damaging inflammatory response.

The molecular heterogeneity of IgA in serum and secretions (reviewed in [10]) is mainly related to its polymerization state. Serum IgA in humans and primates consists mostly of monomeric IgA (88%), which is produced by bone marrow plasma cells, and its concentration in serum is about five-fold lower than that of IgG. By contrast, mucosal plasma cells produce mostly pIgA (80%, mainly dimeric), which is the predominant form of IgA in secretions. The majority of pIgA in secretions is associated with the secretory component (SC) from epithelial origin to form secretory IgA (SIgA). Another difference between the serum and secretory pools of IgA is a relative increase of the IgA2 isotypic form in secretions (especially in the large bowel, but also in the bronchi) as compared to serum. IgA2 lacks most of the hinge region and therefore appears less susceptible to degradation by bacterial IgA-proteases (see later). Finally, IgA2 has two allotypic variants, namely

IgA2m(1) and IgA2m(2), predominating in Caucasians and Africans, respectively. A third IgA2 isotypic form possibly exists on a genetic basis, but this protein has not yet been isolated.

Monomeric IgA (mIgA) is constituted by two light chains (κ or λ), common with other Igs, associated covalently with two specific heavy chains (α chains). An exception is constituted by IgA2m(1), in which light chains form a covalent dimer, noncovalently linked to the heavy chains. The α chain comprises four domains, as for IgG or IgD, and a unique 18 amino acid (aa) carboxyl terminal polypeptide called secretory tail piece (αtp). This tp includes a penultimate cysteine involved in disulphide bonding with the homologous cysteine of the other α chain, or with a cysteine residue of nonimmunological proteins such as albumin or α_1-antitrypsin. Monomeric IgA has a molecular weight of 160 kDa and a sedimentation coefficient of 7S. pIgs are characterized by a high valency of antigen binding sites ($\geqslant 4$), which lead to a great agglutinating capacity of micro-organisms, and by the association with a small 15 kDa polypeptide called the joining chain (J-chain) produced concomitantly with pIgs by mucosal plasma cells. This J-chain includes cysteine residues implicated in IgA (and IgM) polymerization, and is necessary for the transepithelial transport of pIgs. More specifically, the J-chain is not mandatory for polymer formation, but regulates their quaternary structure ("tail-to-tail" model for IgA and ring structure for IgM), which appears to be a determinant for the binding to the epithelial pIgR [11–13]. pIgA is mainly represented by dimeric IgA (335 kDa and 9.5S), whereas higher aggregation states (trimers and tetramers) are also found, usually in smaller proportions. In dimeric IgA, two molecules of IgA are thus linked "tail-to-tail" by the J-chain that bridges one tp of each IgA molecule, while the remaining tps are directly disulphide bound [14]. These disulphide bonds involve the penultimate cysteines located in position 495 in the αtp, which plays an important role in the intrinsic tendency of IgA to polymerize. pIgM (900 kDa and 18S) [15] represents the main form of IgM, in which five molecules of IgM are linked in a ring structure *via* the J-chain that bridges the first to the fifth monomer. However, larger polymers of IgM that are devoid of a J-chain also exist. The heavy chain of IgM (μ chain) also includes a tail piece (μtp), which is highly similar to that of IgA.

Secretory Igs (SIgs) are formed by the association of pIgs produced by mucosal plasma cells with the epithelial SC. This association, elaborated during transepithelial transport, remains noncovalent for IgM, while a disulphide link is usually formed between pIgA (cys^{309}, or sometimes denoted cys^{311}) and SC (cys^{467}) [16]. This association with SC was shown to protect SIgA from proteolytic degradation, although the latter is much less pronounced in the respiratory tract than in the large bowel [17]. In addition, nonsecretory Igs such as mIgA, IgG, IgD or IgE can also reach secretions, mostly by passive diffusion through the endothelial and epithelial tight junctions from submucosal blood capillaries, or from locally infiltrating plasma cells producing these monomeric Igs. Moreover, these monomeric Igs might be cotransported *via* the pIgR, concomitantly with an immune complex involving at least one pIg.

In the gut, an abundant commensal bacterial microflora supports a relatively high proteolytic activity. SIgs and especially SIgA appear more resistant to proteolysis than the other Ig isotypes by their unique structure. Nevertheless, virulent strains of *Streptococcus pneumoniae* or *Haemophilus influenzae* can produce bacterial IgA-specific proteases that specifically cleave the hinge region of IgA1 to produce antigen-binding and crystalline fragments (Fab and Fc, respectively) [18], and this could facilitate the development of infections including in the respiratory tract. Other less classical enzymes, notably from Gram negative bacteria such as some *Pseudomonas* and *Proteus* spp., can cleave serum and secretory IgA1 and IgA2 outside the hinge region. These latter proteases have a broader specificity, sometimes also cleaving IgG. Importantly, these bacterial IgA1-proteases are resistant to inhibition by plasma protease inhibitors (such as α_1-antitrypsin or α_2-macroglobulin), but some can be inactivated by specific neutralizing antibodies present in serum and/or secretions.

Immunoglobulin-A production

Mucosal lymphoid organization. Mucosa-associated lymphoid tissues (MALTs) are organized lymphoid tissues in close relationship with surface and glandular epithelia to constitute both inductive and effector sites of mucosal immune responses. Inductive sites (tonsils, adenoids as nasal-associated lymphoid tissue (NALT), BALT, and Peyer's patches and appendix/colonic-rectal solitary follicles as gut-associated lymphoid tissues (GALT)) are characterized by several follicles where B-cells are preferentially found and contain, after antigenic stimulation, secondary germinal centres. These follicles are surrounded by more diffuse lymphoid tissue (extra-follicular area or T-cell zone) and their luminal side (often called "dome") is covered by the so-called follicle-associated epithelium, which contains microfold cells (M-cells) sampling the antigenic luminal content. MALTs lack afferent lymphatics, which are replaced by specialized high endothelial venules. Conversely, effector sites are represented by the diffuse lamina propria of the different mucosa and exocrine glands, also in striking relationship with the epithelium. Although mucosal and systemic immune systems do not appear totally segregated, MALT has some specific features such as a large predominance of IgA-producing immunocytes.

Several characteristics of the MALT were demonstrated in studies mainly related to the gut, although most of them probably also apply to the respiratory tract. However, a major difference between the airway and digestive mucosa is that MALT and M-cells are virtually absent from the normal respiratory tract [19]. Thus, the organization of the MALT, including M-cell epithelial differentiation is probably induced only when airway and lung tissues are exposed to an increased antigenic load.

B-cell priming in inductive sites. Naive B-lymphocytes enter through high endothelial venules by a multistep process of extravasation into inductive sites (reviewed in [20]). There, they are primed in extra-follicular areas by local CD4+ T-cells, which are activated by interdigitating antigen-presenting cells (APCs) that have processed a luminal antigen [21]. The surface (s) $IgD^+IgM^+CD38^+$ (where $^+$ represents positive expression of a given marker) B-cells, primed *via* these interactions referred to as "first signals", produce an unmutated IgM which can bind the antigen with a low affinity, generating soluble immune complexes that, in contact with follicular dendritic cells, are thought to maintain B-cell memory [22]. Surface IgD^+IgM^+-$CD38^+$ primed B-cells migrate specifically in the dark zone of germinal centres where they proliferate as "founder" Ki-67^+ centroblasts. These "founder cells" are characterized by somatic hypermutation of their Ig variable region genes. This process of hypermutation leads to the expression of an IgM of high affinity for the antigen that rescues these cells from CD95-induced apoptosis by cognate interactions with follicular dendritic cells expressing the processed antigen. Moreover, *via* this high affinity IgM, centroblasts can pick up the antigen and present it to follicular CD4+ T-cells. This interaction requires an additional CD40-CD40 ligand interaction. Finally, activated centroblasts give rise to B-cells that will lead to Ig-producing cells, after a terminal differentiation phase occurring in secretory effector tissues.

B-cell terminal differentiation. Antigen-specific B-cells either lead to memory B-cells ($sIgD^-IgM^+CD38^-B7^+$ B-cells) or initiate isotype switching of their heavy chain constant region (C_H) gene from Cμ to downstream isotypes. This isotype switching, which is associated with high CD38 expression and clonal proliferation, constitutes the terminal phase of B-cell maturation into Ig-producing immunocytes. The "second signals" inducing these events remain poorly defined, but are probably provided by microenvironmental factors such as cytokines released by epithelial or mononuclear cells, and/or cell-to-cell interactions with dendritic cells, as well as topical antigenic exposure (especially in the colon or conjunctiva). Thus, the presence of commensal bacteria plays an important role, since intestinal (and probably bronchial) mucosa from germ-free mice is almost devoid from IgA-producing immunocytes [23]. As supported by the partial IgA deficiency observed in TGFβ1-deficient mice [24], TGF-β has been shown to be a crucial cytokine for IgA switching ("switch factor"), whereas IL-2, IL-5, and especially IL-10 are important (in humans) for clonal proliferation of activated B-cells and terminal differentiation into Ig-producing cells. However, the precise reason why IgA-producing immunocytes represent the predominant mucosal mature plasma cell [25] remains obscure. Moreover, whereas IgA1 represents the predominant isotype, a relative increase of IgA2 expression characterizes mucosal as compared to systemic Ig-producing cells. Alternatively, for IgG-producing mucosal cells (representing about 3 and 20% of the Ig-producing cells in the gut and bronchi, respectively), the predominant isotype is IgG1. Moreover, $IgG3^+$ cells are more frequent than $IgG2^+$ cells in the upper airways, in contrast with the distal gut. IgE-producing plasma cells are virtually absent, except in the mucosa from some allergic patients. Precursors of IgD-producing cells are generated from activated centroblasts characterized by a C_H gene deletion of Cα and Cμ, leading to $SIgD^+IgM^-CD38^+$ cells. This particular subset of centroblasts is frequently found in the upper aerodigestive tract, possibly related to the presence at this level of bacteria such as *H. influenzae* or *Branhamella catarrhalis* producing an IgD-binding protein that can cross-link SIgD. Interestingly, since 90% of IgA^+ (and most IgM^+), as well as 40–100% of IgG^+ and IgD^+ mucosal immunocytes are also J-$chain^+$, J-chain expression represents a relatively early marker of MALT-specific B-cells and thus appears closely related to the homing within the mucosal B-cell system.

Lymphoid recirculation and mucosal homing. Lymphoid recirculation and mucosal homing is reviewed in [26] and [27]. The majority of IgA plasma cells have a half-life of 5 days (as shown in the mouse gut); therefore a continuous supply must be guaranteed by a daily migration and maturation of B-cells into mucosal tissues. Repopulation studies have clearly indicated that mucosal effector immunocytes are largely derived from B-cells initially induced in MALTs. Moreover, a regional specificity characterizes this mucosal homing, since primed B-cells migrate preferentially into effector tissues corresponding to the inductive site where they have been initially stimulated [28]. Further studies established that this specific mucosal homing is supported by specific cell-to-cell interactions between B-cells and endothelial cells in venules of the parafollicular areas (inductive sites) or of the lamina propria (effector sites). The interaction between $\alpha_4\beta_7$ integrin expressed by mucosal B- and T-cells and mucosal addressin cellular adhesion molecule-1 (MadCAM-1, or "mucosal homing receptor"), expressed by mucosal endothelial cells from high endothelial venules [29], has been shown to support in the gut, both the attraction of naive B-cells in inductive sites and emigration of primed B-cells in effector tissues. More specifically, the former is characterized by the interaction between $\alpha_4\beta_7$ integrin associated with L-selectin (CD62 ligand) and a MadCAM-1 molecule with a modified O-glycosylation pattern (fig. 1), while the latter involves the interaction between $\alpha_4\beta_7$ integrin (without L-selectin) with unmodified MadCAM-1. Other general leukocyte-endothelium interactions might also be implicated, such as those between leukocyte function associated molecule (LFA)-1 ($\alpha_L\beta_2$ integrin, CD11a/CD18) and intercellular adhesion molecule (ICAM)-1 or -2, or between very late antigen (VLA)-4 and vascular cell adhesion molecule (VCAM)-1. The molecular interactions underlining the specificity of B-cell migration to the airway and lung mucosa remain unprecised, since $\alpha_4\beta_7$ is well expressed in the airways, but MadCAM-1 is only very weakly expressed by the bronchial endothelium.

Different chemokines released by resident cells regulate the cell trafficking in mucosal tissues. After extravasation, immune cells are directed towards the

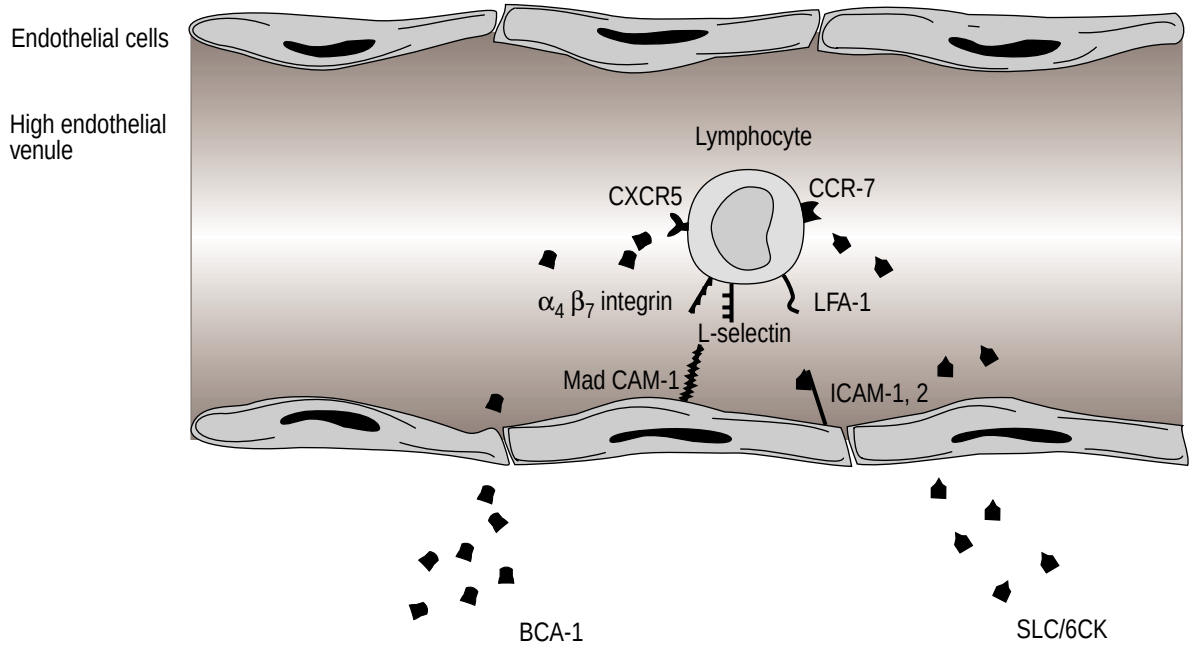

Fig. 1. – Lymphocyte-endothelial cell interactions in high endothelial venules, as identified in gut-associated lymphoid tissues (Peyer's patch). Interaction between $\alpha_4\beta_7$ integrin associated with L-selectin and mucosal addressin cellular adhesion molecule (MadCAM)-1 is required for the mucosal homing of naive lymphocytes in the gut. The other leukointegrin, leukocyte function associated molecule (LFA)-1, interacts with intracellular adhesion molecule (ICAM)-1 or -2 on endothelial cells. The B-lymphocyte chemoattractant (BCA)-1 chemokine attracts in mucosal lymphoid tissues CXCR-5-expressing B-cells, while secondary lymphoid tissue chemokine (SLC)/6CK attracts T-cells through activation of the CCR-7 chemokine receptor.

different lymphoid microcompartments by specific chemoattractants such as B-lymphocyte chemoattractant (BCA)-1, a CXC chemokine attracting B-cells, and secondary lymphoid tissue chemokine (SLC, or Exodus-2), a CC chemokine mainly for T-cells [30] that upregulates the binding of $\alpha_4\beta_7$ integrin$^+$ lymphocytes to MadCAM-1$^+$ endothelial cells, as shown in the gut. Several other mediators have been implicated in the attraction of naive immunocompetent cells into mucosal tissues, such as macrophage inflammatory protein (MIP)-3α (Exodus-1) and 3β (Exodus-3) or stromal cells derived factor (SDF)-1α. Emigration of activated B-cells from germinal centres is probably directed by Ebstein-Barr Virus (EBV)-induced molecule-1 ligand chemokine (ELC) [31]. These molecules act on receptors expressed at the surface of B-cells (or T-cells), such as CXCR-5 for BCA-1 and CCR-7 for SLC. CXCR-5 (and CCR-4) is upregulated on activated CD4+ T-cells, T-helper (Th)1 cells preferentially expressing CCR-5 and CXCR-3 while Th2 preferentially express CCR-3 (or eotaxin R). CD8+ T-cells are probably directed into mucosal tissues by similar signals. Finally, extracellular matrix proteins such as fibronectin, as well as the orientation of reticular fibres, could also play an important role notably through interactions with $\alpha_4\beta_7$ (or $\alpha_4\beta_1$) integrins.

In addition to the regional specialization, the mucosal homing of activated B-cells is characterized by a dichotomy between the upper aerodigestive tract and the gut, since the migration of NALT- or BALT-induced B-cells to the gut is negligible in terms of generating SIgA antibodies [32]. This dichotomy could be related to differences in the adhesion molecules or chemokine profiles mentioned above. A "non-intestinal" homing receptor profile might thus allow the selectivity of homing to the airways (and/or to the urogenital tract), such as interaction of $\alpha_4\beta_7$ integrin with VCAM-1 or L-selectin with its counter-receptor. It is likely that future studies will address and hopefully unravel the mechanisms associated with the lymphocyte homing into the respiratory mucosa.

Putative roles of the epithelium in mucosal immunoglobulin production. The epithelial surfaces represent the putative site of initial antigen encounter. Soluble luminal antigens are probably picked up through the epithelium and further removed from the lamina propria by poorly stimulating dendritic cells. In the gut, luminal particles are preferentially taken up by specialized follicle-associated epithelial M-cells, which are in striking contact with APCs. By contrast, since M-cells have not been identified in the normal respiratory mucosa, the fate of antigens in the airway lumen remains unknown. In addition, both in the airways and in the gut, epithelial cells can provide "second signals" promoting terminal differentiation of B-cells oriented towards IgA production since they can produce different cytokines involved in this process such as TGF-β, IL-5 or IL-10 [33]. In this regard, T-cells are probably not the main source of the cytokines regulating IgA-commitment since IgA production has been shown to be CD4-independent. The epithelium seems thus implicated in most of the different

processes of the mucosal defence including the humoral immune response. Similarly, recent data, including that from studies of the respiratory tract, suggest that the epithelium plays a key role in the pathogenesis of various inflammatory mucosal disorders [33].

Immunoglobulin-A transport

The receptor for pIgs (namely pIgA and IgM) is expressed by mucosal epithelial cells and was initially identified in its soluble form in secretions, hence called "transport piece" and more recently SC. Several lines of evidence indicate, both directly and indirectly, that pIgR, identical to transmembrane SC [9], mediates the transport of pIgs produced in the lamina propria across epithelium into the mucosal lumen. This represents the most active and widespread transcellular protein transport system in the body.

Polymeric immunoglobulin receptor expression. The pIgR is expressed on the basolateral pole of epithelial cells, mainly of the serous type in the gut [34], whereas mucous and ciliated cells also express this surface receptor in bronchi, although to a lesser extent than the serous phenotype [35, 36]. The human pIgR/SC consists in a 100 kDa heavily glycosylated protein of 693 aa which comprises a 18 aa N-terminal signal peptide (encoded by two exons), five Ig-like domains D1–D5 (encoded by four exons), and a sixth extracellular domain, followed by a membrane-spanning segment (23 aa) and a highly conserved cytoplasmic tail (103 aa), all encoded by 5 exons [37] (fig. 2). The 19-kb human pIgR gene, which thus includes 11 exons, is located in chromosome 1 (single locus 1q31–q41) and gives rise to a 3.8 kb messenger ribonucleic acid (mRNA) transcript without alternative splicing. The pIgR promoter region has also been characterized [38, 39] and includes putative binding sites for transcription factors such as interferon (IFN)-γ stimulation response elements (ISREs), binding sites for activating protein (AP)-1 and nuclear factor (NF)-κB, as well as for steroid hormones. The constitutive expression of pIgR appears dependent on a composite site formed by an E-box associated to a partially overlapping inverted repeat sequence. Three types of deoxyribonucleic acid (DNA) response elements in the pIgR gene are involved in the pIgR expression inducible by cytokines: three ISREs (two in the upstream region and one in exon 1) implicated in the response to IFN-γ [39] as well as more weakly to TNF-α [40], a 570 bp region in intron 1 as response element to IL-4 and TNF-α [41], and steroid response element(s) in exon 1 for glucocorticoids and androgens.

The epithelial expression of pIgR appears thus upregulated *in vitro* by different cytokines, especially by IFN-γ both on intestinal epithelial cell lines [42] and the bronchial epithelial cell line Calu-3 [43], as well as on primary bronchial epithelial cells [44], by interacting with specific receptors expressed restrictively on the basolateral pole of these cells. Synergistically with IFN-γ, IL-4 upregulates SC expression on HT-29

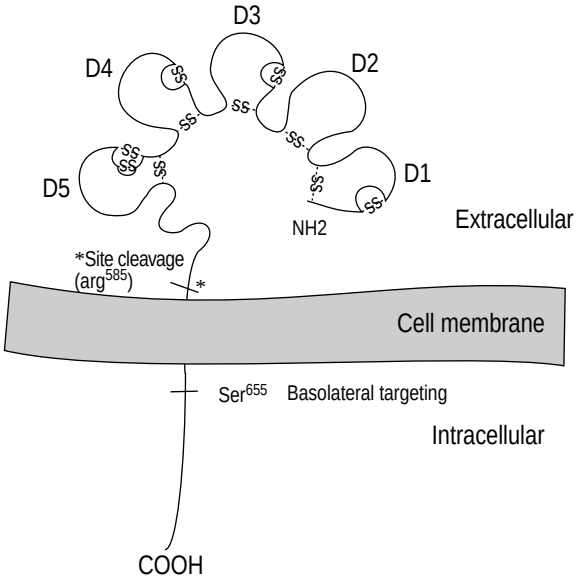

Fig. 2. – Schematic structure of the human polymeric immunoglobulin (pIg) receptor (pIgR)/secretory component (SC) protein. The extracellular part of the pIgR consists in five domains (D1–D5) with Ig-like loops formed *via* disulphide bonds (-S-S-). Additional disulphide bonds are found within the different loops, except in D2. The binding of pIgA implicates the first extracellular domain (D1), while D5 is involved in the covalent bridge with pIgA. SC is the released product of pIgR, the cleavage of pIgR occurring just upstream of the transmembrane segment after an arginine (in position 585), which thus constitutes the last carboxy-terminal amino acid of SC. The cytoplasmic tail includes a phosphorylated serine (in position 655) regulating the basolateral targeting of the pIgR (adapted from [48]). COOH: carboxylic acid.

colon carcinoma cells [42] and Calu-3 cells [45], while the effects of these cytokines appeared additive on IgA transport. TNF-α and IL-1β also enhance SC expression, but to a lesser extent than IFN-γ. Although for some authors [46], the increased SC expression is only partially ascribed to IFN-γ, the observation that SC upregulation is abolished by blocking IFN-γ activity in supernatants from stimulated intestinal mononuclear cells suggests that IFN-γ is the predominant upregulator of pIgR/SC expression [47]. The mechanism of pIgR upregulation by IFN-γ, which is transcriptional and also dependent on *de novo* protein synthesis, has been clearly elucidated (reviewed in [48]). IFN-γ recruits *via* its membrane receptor Signal Transducer and Activator of Transcription (STAT)-1 that once phosphorylated and dimerized, stimulates the transcription of IFN-γ regulatory factor (IRF)-1 that binds to the ISRE in exon 1 of the pIgR gene to promote its transcription. The drastic decrease of SC expression in intestine from IRF-1 deficient mice [49] is consistent with the important role of IRF-1 in mediating the stimulatory effect of IFN-γ on SC gene transcription. Although IRF-1 is also induced by TNF-α, this cytokine exerts its effect mainly through a response element in intron 1 of the pIgR gene. Moreover, conversely with the observations of BLANCH *et al.* [49], ACKERMAN *et al.* [50] found that the level of IL-4- or IFN-γ-induced IRF-1, correlated only weakly with that of SC mRNA, indicating that

IRF-1 independent pathways may be involved in the regulation of pIgR gene transcription by cytokines.

Mechanisms and regulation of transcytosis. The mechanisms and regulation of transcytosis are reviewed in [48] and [51]. After pIgR is synthesized in rough endoplasmic reticulum as a 90–100 kDa precursor protein, it matures to 100–120 kDa after glycosylation in the Golgi complex. A basolateral targeting sequence directs its delivery from the TransGolgi Network to the basolateral membrane where it can eventually bind a J-chain-containing pIg. This sequence is represented by 17 aa comprising a serine (ser^{655}, in human pIgR) which inhibits the basolateral targeting when phosphorylated [52]. The binding of pIgA to pIgR is initiated by a noncovalent interaction between a loop region of the third constant domain of IgA (Cα3) and a conserved sequence in D1 of the pIgR [53]. In contrast with IgM, a covalent disulphide bond is formed during transcytosis and stabilizes the pIgA/pIgR complex (cys^{311} in Cα2 and cys^{467} in D5 of pIgR) [16]. The pIgR, either unbound or complexed with a pIg, is endocytozed, since two tyrosine-based signals direct it to clathrin-coated pits [54], and delivered to basal early endosomes. Under resting conditions, nearly half of the receptor pool is recycled to the basolateral membrane, while 30% is transcytozed in microtubular structures and trapped in apical vesicles without basolateral recycling, to reach the apical membrane. There, the pIgR is released as the SC by a leupeptin-sensitive proteolytic cleavage [55] just upstream from the membrane-spanning segment (after arg^{585}) [56], but the identity of the implicated protease(s) remains unknown. The cleavage releases J-chain-containing pIgA, covalently linked to SC to generate SIgA, whereas IgM is noncovalently complexed to SC to form SIgM. Moreover, since some uncomplexed pIgRs are transcytozed and released, unbound (free) SC is also found in secretions (fig. 3).

The transport of pIgs may be upregulated by an increase of the pIgR transcytotic rate, independently of the level of pIgR expression. Activation of phospholipase C (PLC)-dependent intracellular signals, such as intracellular calcium increase or protein kinase C (PKC) activation, can lead to stimulation of pIgR transcytosis and SC release. Thus, phorbol-myristate-acetate (PMA)-induced translocation of PKC α (and ε) stimulates the pIgR transcytosis and its apical recycling and cleavage in pIgR-expressing Madin Darby Canine Kidney (MDCK) cells [57], and this effect is independent of Ser^{655} phosphorylation. Transcellular routing of pIgR can also be enhanced by calmodulin that binds, in the presence of calcium, to the basolateral targeting signal of pIgR [58]. Other intracellular pathways may also be implicated, such as the phosphatidyl-inositol 3 kinase (PI-3K) pathway, since wortmannin, a PI-3K inhibitor, downregulates pIgR transcytosis by increasing its basolateral recycling after endocytosis. Finally, in contrast with human pIgR, the rabbit pIgR complexed with its ligand appears transcytozed faster than the unoccupied receptor. A stimulation of the rabbit pIgR delivery from apical endosomes to apical membrane mediates this ligand-induced upregulation of pIgR transcytosis, through an intracellular calcium increase, dependent on a tyrosine kinase (TK), further identified as $p62^{yes}$ tk [59], a nonreceptor TK of the sarcoma (src) family.

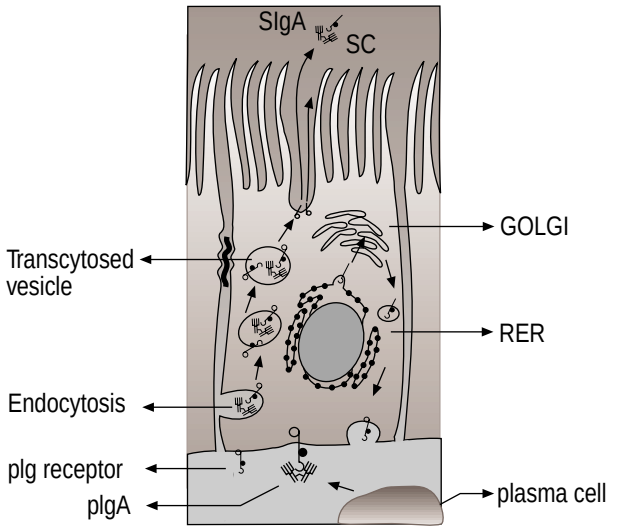

Fig. 3. – Polymeric immunoglobulin (pIg) receptor (pIgR)-mediated transcytosis of pIgA. The epithelial receptor for pIgs, synthesized in the rough endoplasmic reticulum (RER) and heavily glycosylated in the Golgi apparatus, is directed to the basolateral membrane where it can bind its ligand (mostly pIgA). The pIgR/ligand complex is endocytozed in clathrin-coated vesicles. While a significant pool of pIgR is recycled to the cell membrane (not shown), about 30% of the pIgR pool is transcytozed in basal conditions by a microtubular-dependent mechanism towards apical vesicles. The pIgR/pIgA complex is released after cleavage from the apical membrane into the mucosal lumen as secretory immunoglobulin-A (SIgA), while free secretory component (SC) is generated from the constitutive transcytosis of uncomplexed pIgR.

Immunoglobulin-A leukocyte receptor

Identification and characterization of immunoglobulin-A leukocyte receptor. In addition to their important direct role of antigen binding in humoral immunity against infectious agents such as bacteria and parasites, Igs can also initiate and regulate the development of myeloid immune responses through isotype specific Ig receptors, designated FcR. Twenty years ago, surface receptors for IgA designated FcαR were identified on myeloid cells. FcαR, like FcγR (IgG receptors), FcεR (IgE receptors), FcμR (IgM receptors), and FcδR (IgD receptors), are involved in antigen-antibody complex recognition by various cells of the immune system. FcαR recognizes the Fc portion of IgA and trigger cell responses, which, under appropriate conditions, use the same transduction pathways as antigen receptors [60]. In contrast to FcγRs and until now, only one FcαR called CD89 has been cloned from the human monocytic cell line U937 [61] and its cellular distribution has been characterized by the use of monoclonal antibodies against the CD89 cluster [62]. Functional but heterogenous FcαRs have been described to be expressed on monocytes/macrophages [63–66], myeloid cell lines [66, 67], neutrophils [68, 69], eosinophils [70], mesangial cells [71], and probably

on certain lymphocyte populations [72]. The data concerning the expression of FcαR on lymphocytes and on mesangial cells are somewhat contradictory. KERR *et al.* [72] have demonstrated that B- but not T-lymphocytes bind IgA. An IgA receptor could, however, be induced on T-lymphocytes by mitogen or antigen stimulus. Nevertheless, this receptor is different from the CD89 myeloid receptor, as none of the monoclonal antibodies recognizing CD89 bind to T-lymphocytes [72] and recently, PHILLIPS–QUAGLIATA *et al.* [73] demonstrated the presence on T-lymphocytes of an IgA receptor that is more related to the epithelial pIgR than to the CD89 myeloid FcαR. For mesangial cells, the presence of an IgA receptor and FcαR mRNA has also been reported [71]. However, the lack of surface expression of CD89 on cultured mesangial cells, the inhibition of IgA binding by galactose, and the size of this stained protein receptor on sodium dodecyl sulphate-polyacrylamide gel electrophoresis appear to rule out FcαR [74–76]. Finally, while FcαRs appear mostly expressed in PMN, eosinophils and mononuclear phagocytes, these receptors have also been reported to be expressed on mouse hepatic cells [77].

The CD89 gene is localized on chromosome 19 (q13.4) [78] and consists of ~12 Kb [79]. The CD89 complementary DNA (cDNA) codes for an apparent 30 kDa protein with two extracellular Ig-like domains, a single transmembrane domain and a short cytoplasmic tail with no known signalling motifs. FcαRs are heavily, but variably glycosylated proteins with apparent molecular masses of 55–75 kDa on monocytes, macrophages, neutrophils, and 70–100 kDa on eosinophils [69, 70]. Enzymatic removal of N-linked carbohydrate groups allows the identification of the mature CD89 protein,which has a core structure of either 32 or 36 kDa in monocytes, neutrophils and U937 cells, while only the 32 kDa protein is observed in eosinophils [62, 69]. In human alveolar macrophages, a core protein of 28 kDa has been described [80]. Thus, human alveolar macrophages seem to express an FcαR different from that of monocytes and generated by an alternative splicing of the CD89 primary transcript [80]. Indeed, several isoforms of CD89, lacking different parts of the extracellular or transmembrane/intracellular domain and produced by alternative splicing of FcαR transcript, have been described in several cells of the myeloid lineage: macrophages [80], neutrophils [81], and eosinophils [82]. However, the surface expression of a different isoform has only been observed so far in human alveolar macrophages.

FcαR binds all forms of IgA (monomeric, polymeric and secretory IgA of both IgA1 and IgA2 subclasses). Considering the high level of SIgA in secretory fluids, binding of SIgA to FcαR on phagocytic cells is of particular interest with respect to the defence of mucosal surfaces [63]. In addition to FcαR, SIgA has been shown to bind to an unidentified IgA receptor on human monocytes and that binding is blocked by galactose [83]. Moreover, a 15 kDa receptor for secretory component (SC) and thus also for SIgA has been identified on eosinophils but not on neutrophils [84]. Using different CD89 transfectant cell models, several studies have reported that pIgA binds more efficiently to FcαR than mIgA [85]. These data suggest that FcαR probably plays an important role in mucosal as compared to systemic immunity, and notably in the clearance of pIgA immune complexes, phagocytozed by alveolar macrophages and/or hepatic Kupffer cells, while it seems very likely that the clearance of mIgA from the blood occurs through other mechanisms [72]. The spliced variants of CD89, which exhibit different characteristics for IgA binding, may contribute to mIgA binding and clearance by phagocytes.

Association of immunoglobulin-A leukocyte receptor with signalling immunoglobulin leukocyte receptor γ-chain. FcαRs are expressed on the cell surface in association with the FcR γ-chain homodimer [86–88] which is also associated with the FcεRI, the T-cell receptor complex (CD3), the FcγRI (CD64), and some isoforms of FcγRII (CD32) and FcγRIII (CD16) [89]. The FcR γ-chain is associated to the 19 aa transmembrane domain of FcαR where the single positively charged arginine residue at position 209 is necessary for this physical association [88]. FcR γ-chain is neither essential for the binding of IgA to FcαR [85] nor to FcαR expression in transfectants [88, 90]. However, the FcR γ-chain is essential for FcαR-mediated recycling (but not endocytosis), and for triggering the increase of intracellular calcium ions (Ca^{2+}), antigen presentation and cytokine production [91]. The FcR γ-chain also plays an important role in targeting FcαR-bound IgA into endolysosomal compartments, leading therefore to its degradation, while γ-less FcαR-expressing cells, including monocytes and neutrophils, recycle the internalized IgA towards the cell surface. This recycling mechanism could have a physiological significance in regard to the homeostasis of serum IgA concentration by decreasing IgA catabolism [92]. Although the FcR γ-chain is necessary for IgA-induced "outside-in" signal transduction in leukocytes, it is not required for cytokine-induced IgA binding to eosinophils. Thus, the binding of IgA to IL-5-primed eosinophils occurs *via* the intracellular domain of FcαR, independently of its interaction with the FcR γ-chain, through a PI-3K mediated "inside-out" signalling [93].

The FcR γ-chain, but not the FcαR, contains in its cytoplasmic domain, immunoreceptor tyrosine-based activation motifs (ITAMs) that are phosphorylated on tyrosine residues subsequently to FcαR cross-linking [88, 94]. Phosphorylation of ITAMs correlates with the activation of several sets of cytoplasmic protein tyrosine kinases (PTKs) [60]. Src family phosphotyrosine kinases are the first set of these PTKs and in contrast to FcγR, only $p56^{Lyn}$ kinase seems implicated in FcαR/γ-chain signal transduction [95]. Phosphorylation of Src kinases results in the recruitment of $p72^{Syk}$ family member and Bruton tyrosine kinase (Btk) to the FcαR/FcR γ-chain complex [95, 96]. This process leads to the phosphorylation and therefore the activation of further downstream proteins such as PKC, PLCγ [97] and mitogen activated protein kinases (MAPK). Tyrosine kinases could phosphorylate other intracellular proteins such as phospholipid

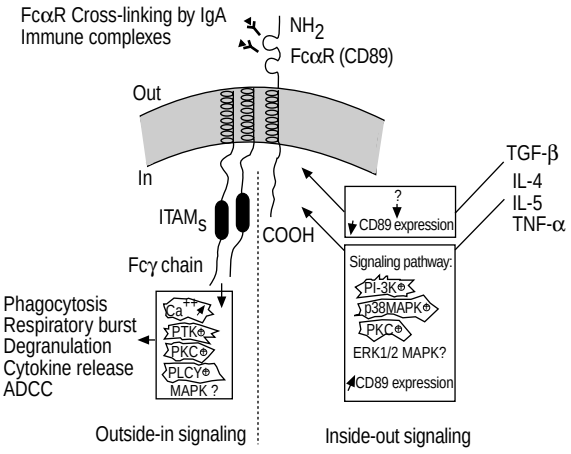

Fig. 4. – Schematic representation of the leukocyte immunoglobulin-A (IgA) crystallisable fragment (Fc) receptor (FcαR) associated with crystallisable fragment receptor FcR γ-chain, and the outside-in and inside-out signalling pathways that regulate functional aspects of FcαR and its expression, respectively (>: increase, <: decrease, ⊕: activation). NH_2: amino group; IL: interleukin; TNF-α: tumour necrosis factor-α; ERK: extracellular signal-regulated kinase; TGF-β: transforming growth factor-β; Ca^{++}: calcium ions; PKC: protein kinase-C; ADCC: antibody-dependent cell-mediated cytotoxicity; COOH: carboxylic acid; Fcγ: crystallizable fragment-γ.

kinases and phospholipases [71]. Signals triggered following phosphorylation of ITAMs could join the biochemical pathways generated by other antigen receptors [60]. These include increased concentration of intracellular Ca^{2+}, activation of PKC and ras pathways that at the end phosphorylate MAPKs, which activate transcription factors regulating gene expression (fig. 4).

Immunoglobulin-A leukocyte receptor expression and regulation. Different mechanisms regulate FcαR expression according to the type of myeloid cell. For example, PMA enhances the expression of FcαR on monocytic cell lines, but not on eosinophils, while a Ca^{2+}-ionophore upregulates FcαR on eosinophils without modulating that on monocytes [70]. Several studies have reported that the expression of FcαR on leukocytes can be either up- or down-regulated by either Th1 or Th2 cytokines and endotoxins, but also by different agents such as phorbol esters, calcitriol, and ionomycin. Chemotactic peptides such as formyl-methionyl leucyl phenylalanine also increase the expression of FcαR on neutrophils, suggesting that this receptor is stored in intracellular pools on the membrane of secretory vesicles [98]. Cross-linking of FcαR with IgA upregulates FcαR expression itself [69, 99]. Table 2 summarizes the modulation of FcαR expression in leukocytes [100–107].

Several molecules involved in the signal transduction pathways subsequent to FcαR activation are now well recognized. Interestingly, the regulation of FcαR expression can also be modulated by an "inside-out" signalling which results in either an increased number of FcαR on the cell surface and/or a higher affinity for their ligands. PI-3K and p38 MAPK, but not MAPKinase/ERKinase–Kinase (MEK) kinases, play for example a critical role in the binding of IgA to IL-4- and IL-5-primed eosinophils [108]. The mechanisms by which PI-3K and p38 MAPK activate FcαR are unknown. However, it is important to outline that these two kinases regulate the cytoskeletal reorganization [109, 110] suggesting, therefore, that cytoskeletal organization may be determinant for FcαR activation. Indeed, cytochalasin D-treated eosinophils fail to bind IgA complexes [93].

In addition to its membrane-bound form, FcαR exists also in soluble forms [111]. These soluble molecules are produced by alternative splicing of the FcαR primary transcript or by proteolysis of the membrane-associated full length receptor. Recent data suggest that monocytes could be the major source for soluble FcαR as PMN do not release it *in vitro* [111]. Soluble FcαR can downregulate FcαR signalling by competing for IgA. This strongly suggests that soluble FcαR is biologically active with a potentially beneficial effect in cases where FcαR/IgA complexes induce cytotoxicity. Soluble FcαR may, therefore, have potential therapeutic effects in IgA-mediated disorders.

Table 2. – Distribution and modulation of the CD89 surface expression on leukocytes

Cells	FcαR		First author [ref. no.]
	Upregulation	Downregulation	
Monocytes/macrophages	TNF-α, IL-1β		SHEN [100]
	GM-CSF, LPS		SHEN [100]
	PMA		MONTERIO [69]
	Calcitriol, IL-3		BOLTZ-NITULESCU [101]
		IFN-γ, suramin	SCHILLER [102]
		TGF-β	RETERINK [104]
PMN	GM-CSF		WEISBART [105]
	TNF-α		GESSL [103]
	IL-8		HOSTOFFER [98]
	f-MLP		SIBILLE [106]
Eosinophils	IL-4, IL-5, GM-CSF		BRACKE [107]

FcαR: leukocyte immunoglobulin-A receptor; TNF-α: tumour necrosis factor-α; IL: interleukin; GM-CSF: granulocyte macrophage-colony stimulating factor; LPS: lipopolysaccharide; PMA: phorbol-myristate-acetate; IFN: interferon; TGF-β: transforming growth factor-β; f-MLP: formyl-methionyl leucyl phenylalanine.

Functions of the mucosal immunoglobulin-A system

The 400 m^2 surface area (300 m^2 and 100 m^2 for the digestive and lung surfaces, respectively) of mucosa continuously in contact with both innocuous and potentially noxious micro-organisms and antigens represent a major challenge for the defence system. IgA-dependent immunity is suggested by several lines of evidence to fit these particular conditions by providing, in cooperation with nonspecific innate factors such as mucociliary clearance, an efficient "first-line" of defence against external agents without inducing a potentially deleterious inflammatory response. The following observations indirectly support the fact that SIgs (mainly SIgA) make a large contribution to this "first-line" mucosal defence by performing a so-called "immune exclusion" of infectious agents from mucosal tissues. The structure itself of SIgA appears to be a compromise between the high cross-linking capacity of pentameric IgM and the great tissue diffusion ability of monomeric IgG. In addition, and especially when the first-line of defence is encompassed, IgA may recruit the inflammatory system by activating FcαR-expressing mucosal leukocytes. On the other hand, an immune tolerance is developed towards innocuous antigens encountering mucosal surfaces.

Protective effects of immunoglobulin-A against infectious agents

Several groups have reported an inhibition of the adherence of bacteria such as *Escherichia coli* to the epithelium by SIgA specific antibodies [112], as well as by free SC. In this respect, it has been shown that SIgA antibodies have a broader specificity than comparable serum antibodies, as supported by deletions and insertions in the complementary determining regions of Ig variable region genes from mucosal immunocytes [113]. The relatively high level of polyreactive "natural" SIgA antibodies is probably designed to assume immediate protection before an adaptive response is elicited, and thus participates to innate immunity [114]. SIgA (as well as free SC) has also been shown to bind to *S. pneumoniae* through a bacterial surface protein called *S. pneumoniae* surface protein A: SpsA [115]. Interestingly, ZHANG *et al.* [116] recently illustrated that the interaction of SpsA with the pIgR on nasopharyngeal epithelial cells mimics the infectious process since it initiates adherence and internalisation of *S. pneumoniae* and its transcytosis towards the basolateral pole were the bacteria are released. This might represent an example of deviation by a pathogen of a mucosal defence mechanism. However, IgA, which was not present in this *in vitro* system might interfere with this process of invasion through its binding to the pIgR.

In addition to the putative luminal exclusion of bacteria performed by SIgA, a specific intraepithelial neutralization of viruses (such as influenza or rotavirus) through interferences with their assembling processes has been demonstrated in pIgR-expressing MDCK cells [117]. Furthermore, it has also been shown that pIgA present in immune complexes (*i.e.* dimeric (d)IgA against dinitrophenyl/bovine serum albumin complex) can be excreted from the basal into apical compartment by confluent monolayers of pIgR-expressing MDCK cells. Thus, IgA appears to be able to neutralize infectious agents or antigens at the three levels of the mucosal tissues: into the lumen ("exclusion" of bacteria), inside the epithelial cell ("neutralization" of viruses), and in the lamina propria ("excretion" of immune complexes). Other anti-infectious properties of SIgA include induction of a loss of bacterial plasmids encoding molecules related to adherence or antibiotic resistance, as well as interference with growth factors (such as iron) or enzymes required for pathogen growth and invasion. It is probably through these different beneficial mechanisms identified *in vitro* that SIgA antibodies have been shown *in vivo* to confer protection to naive mice against oral challenge with *Taenia taeniaeformis* [118], or that many states of resistance to infection are correlated with titres of specific SIgA antibodies [119].

Immunoglobulin-A leukocyte receptor-mediated leukocyte response

In addition to the role of neutralization performed in the mucosa by IgA through its Fab fragment, IgA-containing immune complexes also initiate immune responses that could play a crucial role in host defence, but also in inflammatory diseases. Like the other FcRs associated to ITAMs, cross-linking of FcαR *via* Fc fragments of IgA triggers several biological responses which seem to be dependent on the cell type in the myeloid lineage. These responses, which are generally mediated by Ca^{2+} mobilization and PKC activation [97], include phagocytosis of IgA immune complexes [120, 121], antibody-dependent cell-mediated cytotoxicity [120], killing of IgA-opsonized bacteria and parasites [122–124], and production of reactive oxygen intermediates [64, 125, 126], inflammatory mediators and cytokines [127], as well as leukotrienes and prostaglandins [128]. Cross-linking of FcαR by IgA complexes on monocytes induces an increased production of TNF-α, IL-1β and IL-6 [99, 128–130]. Activation of FcαR may, thus, result in enhanced production of cytokines, which could modulate inflammatory immune responses and tissue infiltration by PMN. The interaction of IgA, and in particular SIgA, with FcαR is also of critical importance in the protection of the epithelial immune barrier. Human IgA can mediate both phagocytosis and postphagocytic intracellular events. This is a relevant effect, especially at mucosal surfaces where the inflammatory response and released cytokines following bacterial adherence and/or invasion can stimulate both FcαR expression and phagocytosis of IgA-opsonized particles by PMN [131]. FcαR also plays an important role in eosinophil degranulation [132] and killing of parasites such as schistosomes [124]. In addition, eosinophils may also bind SIgA *via* a specific receptor for SC and therefore constitute potential candidates in host mucosal defence against parasite invasion. Moreover, it was also shown that SIgA induces

the degranulation of human basophils after priming with IL-3 [133], although no receptor for IgA has been characterized so far on basophils or mast cells.

The triggering of FcαR by IgA is not exclusively associated with the activation of proinflammatory processes such as cytokine release and oxidative metabolism. Several studies have shown that IgA downregulates the oxidative burst and the release of inflammatory cytokines such as TNF-α and IL-6 by activated monocytes [134]. Moreover, in contrast with IgM or IgG, IgA immune complexes exhibit a limited capacity of complement (C) activation. This occurs through the alternate pathway (*via* C3b binding), since IgA complexes fail to activate the C classical pathway [135]. Furthermore, specific IgA can competitively block the IgG-mediated C activation [136]. These FcαR-mediated anti-inflammatory effects are of critical importance in controlling both mucosal and systemic inflammation, protecting host tissues from injury [137, 138]. Indeed, excessive production of cytotoxic oxygen metabolites and inflammatory mediators are often associated with chronic inflammatory diseases such as asthma, chronic obstructive pulmonary disease (COPD), or fibrosing alveolitis. It is, however, important to outline that this FcαR-mediated down-regulation is dependent both on the type of co-stimulatory signals and on the type of effector cell triggered. In this context, the demonstration of spliced variants of FcαR on the surface of the alveolar macrophages is interesting. Although the role of these receptors remains to be defined, they are likely to provide additional regulatory mechanisms of phagocytic and inflammatory responses [80].

Mucosal tolerance

In contrast to the immune response elicited by noxious antigens, probably taken up by efficient M-cells, an inflammatory response against innocuous agents is avoided, particularly in the gut, continuously in contact with food and microflora bacterial antigens. This so-called "oral tolerance" (reviewed in [139]) is recognized as a form of peripheral tolerance in which mature tissue lymphocytes are rendered nonfunctional or hyporesponsive by prior oral administration of antigen. This immune tolerance is also effective in the nasal or bronchial mucosa. Nevertheless, the mechanisms supporting this tolerance towards innocuous and self antigens, which are probably abrogated in coeliac disease as well as in chronic inflammatory disorders of the bowel or the airways, remain poorly understood. They probably involve multiple pathways such as rapid removal of luminal soluble antigens from the mucosa by poorly activating or "tolerogenic" APCs (dendritic cells, naive B-cells, or alveolar macrophages lacking co-stimulatory molecules CD80/CD86 or ICAM-1) [140]. While several studies indicated that CD4+, rather than CD8+, T-cells are required for tolerance induction, CD8+ T-cells primed through human leukocyte antigen (HLA) class I (or CD1)-restricted presentation by epithelial cells have been initially suggested to be the effectors of oral tolerance. Moreover, T-cell receptor (TCR) γδ-expressing CD8+ T-cells have been shown to play an important role, since IgE responses to inhaled antigens in rodent models of nasal or bronchial induced tolerance could be suppressed by the transfer of antigen-specific $\gamma\delta^+$ T-cells [141]. Similarly, *in vivo* treatment with specific anti-TCRγδ antibodies inhibited the induction of oral tolerance in ovalbumin-fed mice [142]. Conversely, FUJIHASHI *et al.* [143] reported an abrogation of oral tolerance by $\gamma\delta^-$ T-cells from the gut epithelium. The Th-cell balance might also be implicated, since oral or nasal tolerance induction is associated with an upregulation of Th2 and a downregulation of Th1 cell activation. However, the subsequent tolerance does not require IL-4 [144]. An active cellular regulation by some particular Th subsets, such as Th3 cells producing mainly TGF-β or IL-10 dependent TGF-β-secreting regulatory T-cells (Tr1 cells), has been implicated, especially after administration of low doses of antigen. Conversely, activated CD4+ T-cells expressing cytotoxic T-lymphocyte-associated molecule (CTLA-4), in contrast to CD28-expressing cells, might provide negative signals leading to T-cell apoptosis, anergy, and down-regulation of Th-cell responses following higher doses of antigen administration [145]. Despite that, the mechanisms underlining both active and anergic immune tolerance have not been completely elucidated, the mucosal route to access a major part of the immune system appears extremely attractive from a clinical standpoint, and should hasten the development of mucosally administered antigens for the treatment of diseases including those of the respiratory tract.

Mucosal immunity in respiratory diseases

Immunoglobulin-A deficiency

A selective IgA deficiency, defined by a serum IgA concentration <0.05 mg·mL^{-1} with normal levels of other immunoglobulin classes, is frequently observed in serum from healthy blood donors with a prevalence of 0.125–0.2%. This inheritable humoral deficiency is not due to defects in the different genes encoding α-chains, but in those regulating the isotype switching. The mucosa from these subjects appears devoid of IgA-producing cells, while an increase of IgG and especially IgM-producing cells is observed with normal migration and maturation of J-chain-expressing B-cells [146]. Although most of these IgA-deficient individuals are healthy, this immunodeficiency is associated with an increased prevalence of atopy [147], or food antigen sensitization [148], as well as recurrent infections (notably in childhood), neoplastic and auto-immune disorders. It is intriguing that allergic and infectious diseases associated with IgA deficiency are mainly located to the respiratory tract. This could be related to the less efficient compensation by IgM observed in the respiratory mucosa as compared to the gut, and/or to a putative proinflammatory activity of IgD, which is predominant in the upper airways. Similarly to IgA-deficient subjects, pIgR-deficient mice, characterized by a total absence of SIgs, appear relatively healthy. However, these mice

exhibit increased concentrations of mIgA and albumin in secretions associated with a plasma leakage and increased concentration of IgG in serum including IgG antibodies against their own *E. coli*, probably related to a deficient epithelial barrier [149]. Moreover, their susceptibility to pathogens and allergens is so far unknown.

Immunoglobulin-A response in chronic airway inflammatory diseases

In contrast to the permanent genetic IgA deficiency, acquired and transient defects of secretory immunity can also occur. Thus, a decrease of IgA^+ plasma cells was observed in the bronchial mucosa from patients who died from COPD as compared with COPD patients who died from other causes, as well as a decrease of IgA in bronchial secretions from heavy smokers [150]. However, variable levels of IgA and SC have been described in airway secretions from smokers and COPD patients, possibly related to the different methods of titration used, or to the potential role of infection. Thus, an increased concentration of sputum IgA in chronic bronchitis was associated with the presence of a clinical respiratory infection [151]. A recent study showed that patients with severe COPD are characterized by a reduced pIgR bronchial expression that correlates with airflow limitation and PMN infiltration [36]. Although consequences of these findings remain hypothetical, it could be speculated that in this acquired deficiency the mechanisms of compensation are not present or inappropriate when the inflammatory response is elicited. Thus, in some susceptible smokers, it is possible that a persistent impairment of the production and transport of secretory Igs, secondary to a decreased pIgR expression, might promote bacterial colonization and thereby PMN infiltration of the airways. The perpetuation of this process could contribute to the progressive remodelling of the bronchial structures as observed in COPD. Moreover, bacteria and PMN are both capable of degrading IgA by proteolytic cleavage [119], leading to a vicious circle of impaired secretory immunity combined with an amplified inflammatory response. Similarly, in patients with cystic fibrosis, a decrease of SIgA in saliva and bronchial secretions has been observed [152]. This observation is in agreement with a study showing that SC expression by the bronchial epithelium from patients transplanted for cystic fibrosis, is strongly decreased as compared with control patients transplanted for primary pulmonary hypertension [153]. However, no significant correlation was found between SC expression and functional parameters in these patients. Thus, secretory immunity seems clearly impaired in COPD and cystic fibrosis, both characterized by chronic obstruction, PMN infiltration, and bacterial colonization of the airways. The epithelial damage associated with these disorders further supports an inefficient first-line of defence with decreased mucociliary clearance and IgA secretion.

The implication of secretory immunity in the pathogenesis of asthma remains more controversial. While the level of SC appeared decreased in the bronchoalveolar fluid from asthmatics [154], many studies observed an increase of IgA production in airway secretions from these patients, possibly related to the release of cytokines such as IL-4 and IL-5 known to upregulate IgA production and transport. In addition, an increased concentration of specific IgA antibodies to both *Dermatophagoides farinae* and *S. pneumoniae* was observed in sputum from *D. farinae*-sensitized asthmatics as compared to controls [155]. In this respect, it has been shown that IgA antibodies to pollen allergens in tears from asthmatics are directed against epitope determinants different from those eliciting IgE synthesis [156]. In asthma and in a wide variety of inflammatory diseases, granulocyte activation is thought to represent a driving force. Since FcαR is largely distributed on granulocytes, IgA could influence the fate of inflammatory diseases such as in macrophage-dependent lung injury [157], dermatitis herpetiformis [158], IgA-nephropathy [159], viral infection through FcαR-mediated uptake of IgA-coated viruses [160], and asthma where eosinophils, particularly in the activated stage [161], could be controlled by IgA-dependent mechanisms. In asthma, IgA, which is present in abundance on mucosal surfaces, is thus able to induce eosinophil degranulation [132], leading to the destruction and/or damage of the respiratory epithelium. Moreover, FcαR expression is increased on eosinophils from allergic individuals [70] and in contrast to healthy donors, eosinophils from asthmatic patients do not need additional cytokine-priming to bind IgA *in vitro* [162]. TNF-α, which has been reported to be implicated in eosinophil-mediated cytotoxicity [163], is abundantly produced in allergic inflammatory diseases [164] and high levels of TNF-α are detected in the bronchoalveolar fluid from asthmatic patients [165]. This is of interest, since TNF-α-primed eosinophils from asthmatic patients bind more IgA than primed eosinophils from normal donors [162]. Moreover, sputum IgA levels from asthmatic patients correlated significantly with eosinophil cationic protein levels [155], suggesting a contribution of IgA to eosinophil activation in asthma. Several other groups focussed their interest on IgA nephropathy, which is characterized by the deposition of IgA (mostly pIgA1) in the renal glomerular mesangial area where receptors for IgA have been reported to be expressed on human mesangial cells [71]. Patients with IgA-nephropathy present delayed plasma clearance of IgA immune complexes and impaired FcαR endocytosis [166]. It has been shown that IgA from these patients is undergalactosylated [167], and this could explain the impaired catabolism of IgA. In the kidney glomerular mesangium, IgA deposition is often associated with IgG, IgM and complement, and results in renal tissue damage. It is not clear whether the production of pro-inflammatory cytokines, mainly TNF-α and IL-6, subsequent to IgA binding to mesangial cells may participate in the amplification of human renal injury. Indeed, and in contrast to the rat model, local inflammation is not associated with increased proliferation of the human mesangial cells induced by IL-6 [168].

Therapeutic applications

Passive immunization with secretory immunoglobulin-A antibodies. Several experimental models have shown that passive immunization with specific pIgA or SIgA can protect animals against various infections, and clinical studies have now been performed [169]. First, IgA purified from human serum, as well as hyperimmune bovine colostrum, which contains, however, mostly IgG antibodies, in addition to SIgA, gave some protection against infections in immunocompromised patients. A promising approach consists of taking advantage of the fact that both J-chain-containing pIgA and SC, in recombinant secretory antibodies, may be produced in the same cell if the appropriate gene transfections have been performed, and that the specificity may be selected by cloning Ig variable region genes from murine monoclonal antibodies. Recombinant anti-*Streptococcus mutans* chimeric SIgA/IgG antibodies produced in plant cells have thus been shown to provide a long-lasting protection against recolonization when applied to tooth surfaces from volunteers [170].

Active mucosal vaccination. In contrast with particulate or replicating antigens, which often induce active mucosal immunity, oral tolerance can potentially be induced by all thymus-dependent soluble antigens, a feature that has hampered the successful development of oral vaccines, notably for autoimmune diseases. Some adjuvants have been shown to promote tolerance, such as conjugation to the B subunit of cholera toxin. Moreover, the possibility to tolerate even a sensitized host has been demonstrated *in vivo* [171]. However, variable results have been obtained so far in clinical trials for disorders such as rhumatoid arthritis, systemic sclerosis or food allergies, notably related to dose-dependent effects.

Polymeric immunoglobulin receptor-targeted gene or protein delivery. Expression plasmids, encoding for example the cystic fibrosis transmembrane regulator (CFTR), complexed to polylysine-linked Fab fragments of antibodies directed against SC, are specifically and efficiently incorporated into pIgR-expressing epithelial cells. This observation has evolved as a potential method of introducing normal copies of the CFTR gene into respiratory cells from patients with cystic fibrosis [172]. However, problems related to the variable level of gene expression or to the route of administration exist for this pIgR-targeted gene therapy, since the plasmids need to be injected in the blood to reach the basolateral pole of the respiratory epithelium and thus cross the endothelial barrier. More recently, a fusion protein consisting of an anti-SC single chain variable fragment (Fv) linked to human $\alpha_1$antitrypsin has been shown to be efficiently transported *in vitro* across respiratory epithelial cells [173]. In addition to its potential application in $\alpha_1$antitrypsin-deficient patients, this fusion protein might provide a potential strategy of delivery of $\alpha_1$antitrypsin into the bronchial epithelial lining fluid from patients with cystic fibrosis, to neutralize neutrophil elastase activity, which probably contributes to the progression of the disease.

Conclusion

A complex network of cells and mediators is required to protect the respiratory tract against various insults, including infection. Immunoglobulin-A was discovered over 40 years ago and was soon identified as the major immunoglobulin in mucosal secretions, at least quantitatively. Despite this, and in contrast with immunoglobulin-G, very little was known about the specific role of immunoglobulin-A in the mucosa. Extensive research has highlighted unique features of the immunoglobulin-A system, particularly related to the protection of mucosal surfaces and the mechanisms regulating immunoglobulin-A active transport at the level of epithelial cells. Together with the recent identification of the immunoglobulin-A leukocyte receptor on phagocytes including alveolar macrophages, increased knowledge of the immunoglobulin-A biology has opened new perspectives for both basic and clinical research that will hopefully lead to the development of novel therapeutic modalities targeted to respiratory disorders.

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