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REVIEW

Transport models for secretory IgA and secretory IgM

P. BRANDTZAEG *Histochemical Laboratory, Institute of Pathology, The National Hospital, Rikshospitalet, Oslo, Norway*

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SUMMARY

At least seven models have been proposed for the epithelial transport of IgA, and each model presents particular features which are not generally appreciated. Much of the confusion in this field has been caused by the many conflicting reports about the cellular origin of the secretory component (SC) and the mode in which it is expressed by secretory epithelial cells. The transport model proposed in 1973–74 on the basis of test-tube experiments and immunohistochemical studies has now gained considerable support from observations made on both normal and neoplastic living epithelial cells. According to this model, the J ('joining') chain and SC represent 'the lock and key' in the selective external translocation of both dimeric IgA and pentameric IgM through serous-type secretory epithelial cells. Incorporation of J chains into these two Ig isotypes during their production in gland-associated immunocytes induces a configurational fit (binding site) allowing them to combine by specific non-covalent interactions with SC in the plasma membrane of the epithelial cell. After being formed on the basolateral surface of the cell, the SC–IgA and SC–IgM complexes are transported in cytoplasmic vesicles to the gland lumen along with some free SC. Covalent stabilization of human secretory IgA during this process depends on unique possibilities for disulphide-exchange reactions and is not an inherent feature of the transport model.

INTRODUCTION

Secretory component (SC) is an epithelial glycoprotein of about 83,000 daltons (Brandtzaeg, 1974a) which contains 18–19% carbohydrate by weight (Sletten, Christensen & Brandtzaeg, 1975) and shows a unique amino acid composition (Cunningham-Rundles, 1978). Dimeric IgA associated with SC is the principal immunoglobulin in human exocrine fluids (Tomasi *et al.*, 1965).

It was speculated in several early studies that SC might facilitate the entry of extravascular IgA into glandular epithelial cells (Tomasi *et al.*, 1965; South *et al.*, 1966; O'Daly, Craig & Cebra, 1971). SC was therefore originally called 'transport piece' (South *et al.*, 1966). This suggestion was prompted by the fact that SC is a regular subunit of the secretory IgA polymer, but there was no obvious explanation for its postulated transport function. Subsequent studies showed that human glandular epithelium exerts transport selectivity not only for dimeric IgA but also for pentameric IgM compared with IgG (Brandtzaeg, Fjellanger & Gjeruldsen, 1968, 1970; Brandtzaeg, 1971a).

We proposed originally that the selective external translocation of IgA and IgM takes place independently of SC, perhaps by means of unique characteristics ('transfer sites') in the heavy chains of these two Ig isotypes and a corresponding epithelial receptor of unknown nature (Brandtzaeg, 1968; Brandtzaeg *et al.*, 1970). This view was mainly influenced by our early failure to

Correspondence: Dr P. Brandtzaeg, Histochemical Laboratory, Institute of Pathology, The National Hospital, Rikshospitalet, Oslo 1, Norway.

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demonstrate a regular association between SC and secretory IgM (Brandtzaeg *et al.*, 1968; Brandtzaeg, 1971a). Also, the observation that pure glandular fluids contain about 10 times more monomeric IgA than IgG indicated that the transport mechanism was specific for the IgA isotype rather than for dimeric IgA (Brandtzaeg *et al.*, 1970). By analogy, an epithelial receptor specific for IgG1 has been demonstrated in bovine mammary glands, which preferentially transmit this Ig unchanged from serum during the colostrum-forming period (Kemler *et al.*, 1975). The intestinal epithelium of some suckling animals likewise contains a specific receptor that mediates the translocation of intact IgG from the gut lumen into the blood circulation (Rodewald, 1976).

It should be stressed from the outset that the possible existence of an as yet undefined glandular Fc receptor specific for the heavy chains of human IgA and IgM has not been definitely excluded. Nevertheless, studies during the first part of the last decade made it increasingly likely that specific epithelial uptake of Ig is mediated by SC. It seemed justified, therefore, in 1973 to propose a common glandular transport model for dimeric IgA and pentameric IgM (Brandtzaeg, 1973a, 1973b); it was suggested that plasma membrane-associated SC, by selective non-covalent affinity for these two J chain-containing Ig polymers, determines their uptake by serous-type secretory epithelial cells. This model was further elaborated in two subsequent publications (Brandtzaeg, 1974b, 1974c).

VARIOUS MODELS PROPOSED FOR EPITHELIAL IgA TRANSPORT

In the first model proposed for glandular transport of IgA (Tomasi *et al.*, 1965; South *et al.*, 1966) it was envisioned that SC-producing epithelial cells mediated the Ig transport, and that the union of two IgA monomers took place by intracellular complexing with SC (Fig. 1). The IgA monomers were thought to be produced by local plasma cells, but a contribution from serum was not excluded. It was not clear whether the epithelial transport was active, or whether it depended on high concentrations of locally formed IgA. This model was more recently supported by Shiner & Ballard (1973) using commercial immunofluorescent antibodies to 7S monomeric IgA, 11S secretory IgA, and SC. However, their results are questionable since the reagents obviously did not discriminate between monomeric and dimeric IgA, nor between free and bound SC.

Heremans & Crabbé (1967), on the basis of immunohistochemical studies, challenged the view that IgA follows an intracellular route through the epithelium, and suggested that the apical IgA fluorescence seen in intestinal glands should be ascribed to adsorbed mucus rather than to cytoplasmic IgA. They stressed the localization of IgA in the epithelial interstices, and proposed that most intestinal IgA diffused between the epithelial cells into the gut lumen where complexing with SC and thereby polymerization of IgA took place (Fig. 1). It was still unknown at that time that gland-associated plasma cells produce mainly dimers of IgA (Brandtzaeg, 1973b, 1974d, 1974e).

A direct passage of IgA into the lumen would be restricted by the apical tight junctions between the epithelial cells. Tomasi and co-workers (Tourville *et al.*, 1969; Tourville & Tomasi, 1969; Franklin, Kenyon & Tomasi, 1973), therefore, maintained the view that the complexing between IgA and SC took place in the epithelial interstices so that the completed secretory IgA molecule entered the glandular cell and was subsequently extruded into the lumen (Fig. 1). This transport model left many questions unexplained. How could the basement membrane preferentially allow IgA (and IgM) rather than IgG to diffuse into the epithelial interstices? Why was SC usually undetectable in sera of hypogammaglobulinaemic individuals (Brandtzaeg, 1971c) if it was regularly secreted into the intercellular spaces? How could the secretory IgA molecules be taken up by the epithelial cell? These authors (Tourville *et al.*, 1969; Tourville & Tomasi, 1969), moreover, claimed that the mucous-type glandular cell was especially active in the production of SC, but it was not discussed how this observation was included in their transport model.

Allen, Smith & Porter (1973) tried to follow the intestinal secretion of IgA in pigs at the ultrastructural level. They suggested that pseudopodia from plasma cells adjacent to the glands were sloughed off as vesicles which crossed the basement membrane into the epithelial interstices and thereafter entered the columnar cells (Fig. 1). It was thought that IgA in this way could be protected during the entire external translocation. After being released into the gut lumen, IgA

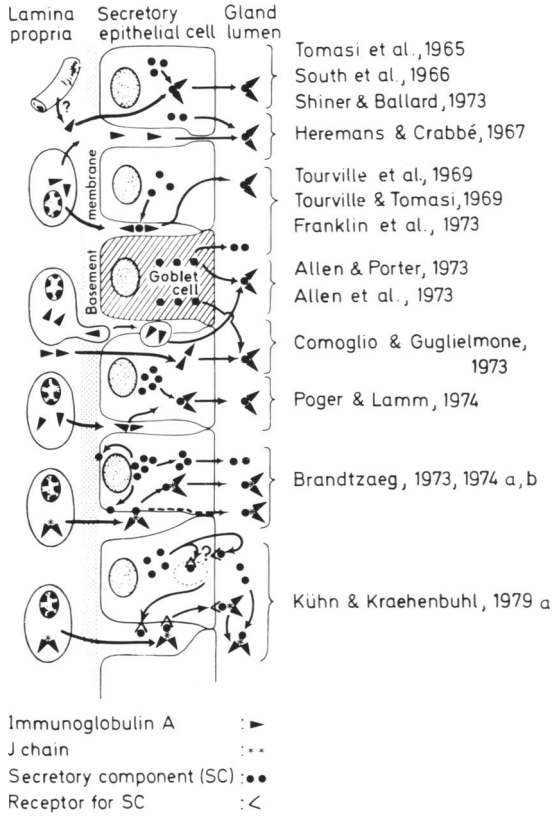

Fig. 1. Schematic representation of the generation and epithelial transport of secretory immunoglobulin A as proposed by various research groups. Each model presents particular features, which are discussed in detail in the text.

would combine with SC, which also according to the latter authors was derived mainly from goblet cells and was not involved in the transport of IgA (Allan & Porter, 1973). This model is incompatible with the fact that secretory IgA may be transported through glands that are located at a considerable distance from the IgA-producing cells (Brandtzaeg & Baklien, 1977).

Comoglio & Guglielmone (1973) likewise claimed, on the basis of immunohistochemical studies in the mouse, that SC was produced by goblet cells whereas IgA was translocated through columnar epithelial cells. Since it was postulated that the union between SC and IgA took place in the gland lumen (Fig. 1), it was thought that the function of SC was not to mediate the IgA transport but, instead, to anchor IgA to the glycocalyx at the luminal epithelial surface.

The subsequent immunohistochemical study of Poger & Lamm (1974), on the other hand, identified clearly the serous-type columnar epithelial cell as the major source of SC, in accordance with independent studies from our laboratory (Brandtzaeg, 1973a, 1974b). Also in agreement with our studies (Brandtzaeg, 1974c), SC was found to exist in a free form in the Golgi zone but was partially complexed with IgA in the apical part of the columnar epithelial cell. Nevertheless, since Poger & Lamm found no indication of plasma membrane-associated SC, their observations were interpreted (Lamm, 1976) to suggest that the assembly of secretory IgA took place inside the epithelial cell after the fusion of pinocytotic vesicles and SC-containing Golgi vesicles (Fig. 1).

If the epithelial uptake of IgA, according to the model of Poger & Lamm (1974), should occur as 'fluid' or 'bulk' pinocytosis, it would be difficult to explain the selectivity for IgA and IgM. One possibility mentioned by Lamm (1976) was that SC protected IgA against degradation by intracellular enzymes, whereas IgG and other proteins included in the pinocytotic vesicle were degraded. Even fragments of IgG should retain some antigenicity, however, and the complete lack

of cytoplasmic IgG staining in glandular epithelia speaks against an entry of this protein into intact secretory cells (Brandtzaeg, 1974b; Brandtzaeg & Baklien, 1976a, 1977). Also, secretory IgM contains SC in a more 'open' quaternary structure than secretory IgA (Brandtzaeg, 1975a), and IgM is apparently not protected against proteolytic degradation by its combination with SC (Richman & Brown, 1977) in the way described for dimeric IgA (Lindh, 1974).

Dimeric IgA and pentameric IgM will, according to our transport model (Brandtzaeg, 1973a, 1973b, 1974b, 1974c), be selected at the basolateral epithelial cell membrane owing to the SC-binding site of these J chain-containing polymers (Fig. 1). It is proposed that the receptor–Ig complexes formed on the cell surface are either taken up by adsorptive pinocytosis or may partially float in the plasma membrane and reach the gland lumen without entering the cytoplasm (broken arrow in Fig. 1). Which route is preferred may depend on the cellular distribution of SC, which apparently varies among different glands (see section below).

SC is disulphide-linked in 75–80% of human 11S secretory IgA (Brandtzaeg, 1971b, 1977b), and Lamm (1976) pointed out that there is no other known situation where a receptor becomes permanently attached to the transported molecule. This is probably no valid argument against a receptor function of SC in the glandular transport of IgA and IgM, however. Stabilization of SC–Ig complexes, as regularly seen for human dimeric IgA, apparently depends on the production of a surplus of free SC and unique possibilites for disulphide-exchange reactions (Brandtzaeg, 1977b). In normal human saliva and colostrum the amount of free SC may approach that of bound SC (Brandtzaeg, 1973a), whereas in pig colostrum there are only traces of free SC and 60% of the dimeric IgA lacks SC after purification (Bourne, 1974). SC is likewise retained in only 60–70% of purified human secretory IgM (Brandtzaeg, 1975a), and SC–IgM complexes formed *in vitro* show very little or no tendency to stabilization by disulphide-exchange reactions (Brandtzaeg, 1974d, 1977a; Weicker & Underdown, 1975; Lindh & Bjørk, 1976a). In this respect human IgM is also similar to rabbit IgA of the subclass *g* (Knight, Vetter & Malek, 1975). A covalent interaction with SC thus seems to be a unique characteristic of human IgA instead of being an inherent feature of the proposed transport model.

The function of SC has been confused further by the suggestion that it may act as a γ-glutamyltransferase in the glandular transport of IgA (Binkley & Wiesemann, 1975). However, we and others have distinctly separated the γ-glutamyltransferase activity of colostrum from free SC and secretory IgA (Brandtzaeg & Winsnes, 1976; Labib, Calvanico & Tomasi, 1976; Lindh & Bjørk, 1977a). The only established activity of SC is thus to complex spontaneously with J chain-containing IgA and IgM by specific non-covalent interactions (Eskeland & Brandtzaeg, 1974; Brandtzaeg, 1976a); this property is certainly compatible with its proposed epithelial receptor function.

Weicker & Underdown (1975) argued against a participation of SC in glandular Ig transport by referring to the lack of *in vivo* (Newcomb & Ishizaka, 1970) and *in vitro* association between SC and IgE (Brandtzaeg, 1977a). Neither is this argument valid, however, since the previous assumption of selectivity in the external transfer of IgE comparable to that of IgA does not hold true (Nakajima, Gillespie & Gleich, 1975). A relative enrichment of IgE in some exocrine fluids compared with serum apparently depends on local synthesis combined with passive diffusion through epithelial interstices as part of pathotropic potentiation of mucosal immunity (see Hanson & Brandtzaeg, 1980).

In the transport model proposed on the basis of studies in our laboratory (Brandtzaeg, 1973a, 1973b, 1974b, 1974c) it was not possible to suggest how SC could reach the plasma membrane of the epithelial cell, although it was implied that, when operating as a receptor, SC was an integral membrane protein. However, the question of the routes of intracellular transport of secretory products from the rough endoplasmic reticulum to the plasma membrane remains vexed (see Newmark, 1979). Recent extensive studies with isolated rabbit mammary cells have supported the proposed role of SC as an epithelial receptor for dimeric IgA (Kraehenbuhl & Kühn, 1978; Kühn & Kraehenbuhl, 1979a). In addition, these authors proposed that SC reaches the basolateral plasma membrane by some unexplained mechanism after initial secretion and binding to a luminal receptor specific for free SC (Fig. 1). The alternative possibility that free SC encounters its membrane receptor in cytoplasmic vesicles was also considered (Fig. 1). It remains to be shown, however, that a receptor truly specific for SC is present in the plasma membrane of all types of secretory epithelial cells and in all species.

The suggestion made by the same authors (Kraehenbuhl & Kühn, 1978; Kühn & Kraehenbuhl, 1979a) that the final luminal release of dimeric IgA takes place due to displacement by free SC (Fig. 1) can definitely not hold true in the human species where dimeric IgA becomes linked by disulphide bridges to SC during the glandular transport; by immunohistochemistry it has been indicated that this covalent stabilization of secretory IgA begins already at the level of the basolateral plasma membrane (Brandtzaeg, 1974c, 1978), and that there is a continual SC–IgA association during the intracellular vesicular transport (Nagura *et al.*, 1979a). It has been substantiated *in vitro* that although a considerable amount of bound SC can be displaced from human SC–IgM complexes by addition of a large excess of free SC, this is not so for human SC–IgA complexes (Brandtzaeg, 1977b).

EVIDENCE FOR SC-MEDIATED TRANSPORT OF IgA AND IgM

SC–Ig interactions

Mach (1970) and Radl *et al.* (1971) independently reported that an IgA–dimer conformation is essential to produce SC–IgA complexes *in vitro*. Complexing with IgM was also noted in these studies, but only polymers larger than 19S pentamers were thought to be active (Radl *et al.*, 1971). The latter observation could not be confirmed in our laboratory (Brandtzaeg, 1974d). By contrast, it was shown that SC was able to combine with pentameric IgM as readily as with dimeric IgA, and that the initial complex formation depended on non-covalent interactions rather than on the formation of disulphide bonds (Brandtzaeg, 1974d, 1977b). This observation was crucial for the proposed receptor function of membrane-associated SC, and has been confirmed independently by two other research groups (Weicker & Underdown, 1975; Socken & Underdown, 1978; Lindh & Björk, 1976a, 1976b, 1977b).

When Mach published his results in 1970, the J chain (about 15,000 daltons) had just been detected in polymeric IgA and IgM (for review, see Inman & Mestecky, 1974; Koshland, 1975); in an addendum to his paper he, therefore, postulated a role for this polypeptide in the SC-binding process. We obtained the first evidence to substantiate such a function of the J chain when we found that both IgM and IgA polymers lacking J chain failed to bind SC *in vitro* (Eskeland & Brandtzaeg, 1974; Brandtzaeg, 1976a). The report of Jerry, Kunkel & Adams (1972) has caused some confusion in this respect. They found that in the presence of a large excess of SC obtained from reduced secretory IgA, covalent complexing took place with monomeric IgA of the subclass α_2 and genetic variant Am_2 (+). It has also been reported that bovine SC, added in large excess, to some extent may become covalently complexed with certain J chain-deficient IgA polymers *in vitro* (Tomasi & Czerwinski, 1976). These findings must be clearly distinguished from our results which are based on non-covalent interactions with small amounts of native human SC.

Although it seems justified to conclude that the J chain is mandatory for specific combination of SC with dimeric IgA and pentameric IgM, it is not clear how this polypeptide is involved in the binding process. A direct interaction between SC and J chain is not likely since the purified dimeric polypeptide shows only marginal blocking of the binding of SC to the Ig polymers (Brandtzaeg, 1975b).

Weicker & Underdown (1975) initially reported that IgM pentamers and IgA dimers bind SC with similar affinity. Conversely, in our laboratory a much stronger non-covalent interaction was found between pentameric IgM and SC than between dimeric IgA and SC (Brandtzaeg, 1974d), and the apparent equilibrium constant of association (K_a) was estimated to be 2·7–12·5 times higher for IgM than for dimeric IgA (Brandtzaeg, 1977b). Socken & Underdown (1978) subsequently confirmed these results by reporting that the binding constant of SC for IgM was 2–5 times higher than for dimeric IgA. It remains to be clarified if the different properties of the SC-binding sites in the two types of human polymers reflect a 'bonus' effect of a higher molar J chain content in IgM, as indicated by recent immunochemical quantitations (Brandtzaeg, 1975c; Grubb, 1978).

Three independent research groups have now determined the affinity (K_a) of SC for J chain-containing Ig polymers to be about 10^8 M^{-1} (Brandtzaeg, 1977b; Socken & Underdown, 1978;

Kühn & Kraehenbuhl, 1979b), which is similar to values obtained for a variety of antigen–antibody reactions. Nevertheless, 10^8 M^{-1} is probably an underestimate when it comes to interactions with SC present in epithelial plasma membranes. Schiff, Dorrington & Underdown (1980) recently reported that SC-binding experiments in dilute solution, and kinetic measurements with anti-Ig Sepharose to separate SC complexes, indicated a $K_a \geq 10^{10}$ M^{-1}. In experiments with binding of dimeric IgA to dispersed rabbit mammary cells, Kühn & Kraehenbuhl (1979a 1979b), moreover, found that the association and dissociation rates were faster and K_a higher (10^9 M^{-1}) than that obtained with SC in solution (10^8 M^{-1}). These studies suggested that membrane-bound SC is modified, probably by a configurational change favouring its interaction with Ig polymers.

Compared with disulphide exchange reactions *in vitro* (Brandtzaeg, 1977b), the covalent stabilization of SC–IgA complexes taking place during glandular transport must be very efficient. This process is probably enzymatically catalysed in the secretory epithelial cells. A disulphide-exchange enzyme obtained from rat liver microsomes has been found to promote the binding of human SC to dimeric IgA and also to induce some covalent stabilization of SC–IgM complexes (Murkofsky & Lamm, 1979). The proneness for covalent stabilization of SC–IgA complexes probably contributes to the functional advantage of secretory IgA compared with secretory IgM (Haneberg, 1974a, 1974b); but it is nevertheless the primary non-covalent interactions with SC that reflect the potential receptor function of this epithelial glycoprotein. The superior affinity of pentameric IgM for SC may thus confer a secretory advantage on this Ig, which may be of benefit in the newborn and in selectively IgA-deficient subjects, whose local IgM responses are prominent in the intestinal mucosa (see Brandtzaeg, 1981).

Characteristics of gland-associated immunocytes

The first direct evidence that the predominating IgA immunocytes in glandular sites produce mainly dimers, was obtained by an SC-binding test developed on tissue sections (Brandtzaeg, 1973b). This finding was subsequently supported by our immunohistochemical localization of J chain in the cytoplasm of 80–100% of IgA immunocytes in normal glandular sites (Brandtzaeg, 1974e, 1976b; Brandtzaeg *et al.*, 1979; Korsrud & Brandtzaeg, 1980). These figures were obtained from tissue sections treated with acid urea (Brandtzaeg, 1976b). In the parotid gland, for example, such treatment raised the J chain positivity of IgA cells from 54 to 93%, and the staining intensity was also increased (Korsrud & Brandtzaeg, 1980). The cytoplasmic J chains thus seem to be partially concealed in most of the cells due to combination with IgA subunits.

This observation was confirmed at the ultrastructural level as we obtained enhancement of J chain antigenicity in the endoplasmic reticulum of intestinal immunocytes after exposure to acid urea (Nagura *et al.*, 1979a). Along with the previously noted diffuse cytoplasmic affinity for SC (Brandtzaeg, 1973b, 1974d), these findings prove that a substantial completion of dimeric IgA normally takes place in the endoplasmic reticulum. Glandular IgM-producing cells likewise contain J chain and express cytoplasmic affinity for SC (Brandtzaeg, 1973b, 1974d, 1976b; Brandtzaeg *et al.*, 1979; Korsrud & Brandtzaeg, 1980).

Furthermore, about 40% of the IgG immunocytes and most IgD immunocytes in glandular sites produce J chains (Brandtzaeg, 1974e; Brandtzaeg *et al.*, 1979; Korsrud & Brandtzaeg, 1980). However, J chains do not combine with IgG and are not secreted from the IgG cells but become degraded intracellularly (Mosmann *et al.*, 1978). Although not examined, the same probably holds true for J chains in IgD immunocytes. The significant biological consequence of the striking J chain production shown by glandular immunocytes thus appears to be that IgA dimers and IgM pentamers with SC-binding sites are generated locally and readily available for complexing with SC present in nearby secretory epithelial cells.

Immunohistochemical observations

Many conflicting reports have appeared about the cellular origin of SC (see Brandtzaeg & Baklien, 1977). Our studies have distinctly demonstrated SC in the intestinal columnar crypt cells, but we have been unable to find it associated with the mucinous content of goblet cells (Brandtzaeg, 1973a,

1974b). Nevertheless, occasional faint specific staining is seen in mucinous acini of salivary and respiratory glands, especially related to the periphery of the cells (Brandtzaeg, 1977a). It has likewise been difficult to exclude at the ultrastructural level that small amounts of SC are present at the lateral borders of intestinal goblet cells (Brown, Isobe & Nakane, 1976). Moreover, Poger, Hirsch & Lamm (1976) reported that some well-differentiated villous colon carcinomas contained SC and mucin in the same cells. Also, goblet cells of gastric epithelium with a moderate degree of intestinal metaplasia and signet-ring cells of gastric carcinomas have been reported to contain SC (Maeda, 1977).

The immunofluorescence staining patterns from our studies indicate that in respiratory glands there are high concentrations of SC both in the cytoplasm and in the plasma membrane of serous acini and duct cells; in salivary glands there is a faint cytoplasmic fluorescence and more distinct staining related to the cell borders; but in the intestinal epithelium the cytoplasm is more intensely fluorescent than the cell periphery. In the small bowel, SC is characteristically present in the columnar cells of the crypts of Lieberkühn, and decreases in concentration in the epithelium covering the villi, whereas in the large bowel it is generally present also in the columnar surface-lining cells (Brandtzaeg, 1974b, 1974c, 1977a; Brandtzaeg & Baklien, 1977). Recent immunoelectron microscopic studies have substantiated that not only do the intestinal columnar cells synthesize SC, as demonstrated by its localization in the endoplasmic reticulum, but that they also clearly contain SC in the basolateral plasma membrane (Brown *et al.*, 1976; Jos *et al.*, 1979).

In most normal mucosal specimens the lamina propria contains much less extracellular IgA than IgG, despite extensive local synthesis of the former (Brandtzaeg, 1974b; Brandtzaeg & Baklien, 1976a). This is compatible with an efficient epithelial transport of the locally produced dimeric IgA, which usually appears both in the cytoplasm and in relation to the basolateral borders of serous-type glandular cells. As described for SC, the latter staining feature is especially marked in respiratory and salivary glands. The epithelial distribution of IgM mimics that of IgA, but the staining is normally fainter and readily demonstrable only in the large bowel (Brandtzaeg, 1975a), as also noted by others in normal (Chen, 1971) and especially in IgA-deficient individuals with enhanced local synthesis of IgM (Heremans & Crabbé, 1967; Savilahti, 1973).

We have interpreted the fluorescence staining for IgA and IgM appearing at the lateral cell borders as related to the plasma membrane (Brandtzaeg, 1974b, 1974c), and ultrastructural studies have confirmed such a localization in intestinal columnar cells (Brown *et al.*, 1976; Jos *et al.*, 1979). Specific staining for IgD and IgE in glandular epithelia has never been seen in our laboratory (Brandtzaeg & Baklien, 1976b).

Our immunohistochemical studies of neoplastic glandular cells have strongly supported the role of SC in the selective epithelial uptake of dimeric IgA and pentameric IgM. When the epithelial fluorescence for SC and IgA in 41 large bowel adenocarcinomas was scored on a semiquantitative scale, the results showed that the concentrations of both components were significantly related to the histological tumour grade (Rognum *et al.*, 1980). Thus, the amounts of cytoplasmic SC and IgA were well correlated. We have also studied in detail a case of infiltrative gastric carcinoma composed of signet-ring cells containing SC along with mucin and carcinoembryonic antigen (Brandtzaeg & Rognum, unpublished observations). In contrast to previous reports (Maeda, 1977; Ejeckam *et al.*, 1979), both IgA and IgM along with J chain were clearly localized in the cytoplasm of the tumour cells, whereas most of them were completely devoid of IgG.

Studies of living cells

The first direct evidence that J chain-containing dimeric IgA and pentameric IgM combine with SC on the surface of secretory epithelial cells came from studies of dispersed normal human colonic columnar cells (Brandtzaeg, 1978). A substantial fraction of the isolated cells contained free SC and secretory IgA in a cytoplasmic distribution that corresponded to the reported immunohistochemical results discussed above. On their surface the same cells were shown to bear SC complexed with J chain-containing IgA, whereas only small amounts of free SC were found. IgM was detected where the largest concentrations of IgA and SC occurred.

SC is thus normally exposed on the plasma membrane of columnar epithelial cells. This fact

strongly supports its proposed receptor function, which has been further substantiated by studies carried out on an epithelial cell line (HT-29) established from a human colon carcinoma. In long-term tissue culture most of these neoplastic cells express SC both in the cytoplasm and on the plasma membrane (Huang, Fogh & Hong, 1976). J chain-containing polymeric IgA and IgM, but not monomeric IgA and IgG, will bind to the surface of these cells (Crago *et al.*, 1978). Moreover, ultrastructural studies have shown that the bound dimeric IgA becomes internalized by pinocytosis when the cells are incubated at 37°C; the vesicles are subsequently transported through the cytoplasm and are finally discharged across the apical surface (Nagura, Nakane & Brown, 1979b). These observations were recently extended in experiments with dispersed epithelial cells and plasma membrane-enriched fractions obtained from mammary glands of midpregnant rabbits (Kühn & Kraehenbuhl, 1979a); it was found that addition of ^{125}I-labelled dimeric IgA resulted in a saturable, reversible time- and temperature-dependent binding process, and the binding capacity accorded with the density of free SC on the plasma membranes.

CONCLUSIONS AND PERSPECTIVES

Although the model proposed for SC-mediated epithelial Ig reception and translocation (Fig. 2) was originally based on test-tube experiments with purified proteins and on immunofluorescence studies of dead tissues, it has recently gained strong support from observations made on both normal and neoplastic living epithelial cells. It should be pointed out, however, that despite the attractive possibility that the J chain and the epithelial SC represent 'the lock and key' in the selective external transport of dimeric IgA and pentameric IgM, it has not been definitely excluded that the epithelial cells express isotype-specific Fc receptors for IgA and IgM. Dimers of IgA could even in that case have a significant transport advantage over monomers, owing to their double number of binding sites. Thus, the Fc receptors present on human polymorphonuclear granulocytes show strikingly higher binding activity for dimeric than for monomeric IgA (Fanger *et al.*, 1980). On the other hand, it may be argued that the enrichment of monomeric IgA compared with IgG seen in pure glandular secretions (Brandtzaeg *et al.*, 1970) is due to a combination of passive diffusion and degradation. Intercellular diffusion through epithelia probably includes monomeric IgA derived both from serum and from the abundant local IgA-producing immunocytes, which most likely release monomers in addition to dimers (Bull, Bienenstock & Tomasi, 1971). Some breakdown of secretory IgA is also possible, and may explain why a fraction of the monomeric IgA present in colostrum apparently is associated with SC (Mestecky, Kraus & Voight, 1970).

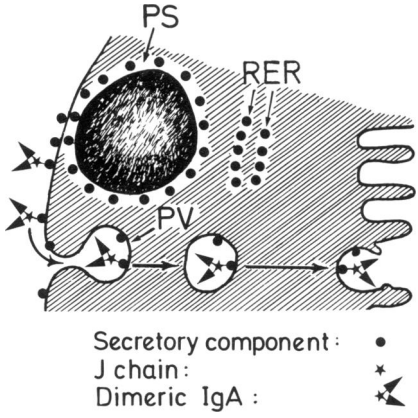

Fig. 2. Transport model based on a 'lock and key' function of secretory component (SC) and J chain in the glandular reception and translocation of dimeric IgA, from the formation of SC–IgA complexes in the basolateral plasma membrane (*left*) of the serous epithelial cell to the luminal extrusion of pinocytotic vesicles (*right*) containing completed secretory IgA and some free SC. RER = rough endoplasmic reticulum, PS = perinuclear space, PV = pinocytotic vesicle.

Altogether it seems unlikely that complexing of dimeric IgA and pentameric IgM with epithelial SC is merely an epiphenomenon serving to stabilize the secretory immunoglobulins. The biological significance of the primary non-covalent SC–Ig interactions is apparently the selective epithelial reception of J chain-containing polymers. A redistribution of the innate membrane SC seems to take place after these interactions (Brandtzaeg, 1978); this may reflect the initial step in the external translocation of the SC–Ig complexes, since it is known that complexing in plasma membranes stimulates pinocytosis (Raff, 1976). However, endocytic invaginations of the plasma membranes are found also in columnar epithelial cells in patients lacking IgA and IgM; it has, therefore, been proposed that an inherent tendency of SC-containing vesicles to migrate from the basolateral membrane to the apical surface explains the normal external translocation of SC–IgA and SC–IgM complexes (Nagura, Nakane & Brown, 1980).

Further aspects of the proposed transport model remain obscure. Firstly, it is not known how SC is incorporated into the plasma membrane. The immunoelectron microscopic micrographs published by Brown *et al.* (1976) indicated that the SC-containing perinuclear space and the external plasma membrane sometimes are fused (Fig. 2); SC might hence be externalized by mobilization of an internal cell membrane. The appearance of SC 'blebs' on the surface in the nuclear region of cultured normal columnar epithelial cells is consistent with this possibility (Brandtzaeg, 1978). In this case membrane-bound and secreted free SC may well be the same gene product. As discussed above (Fig. 1), results of recent experiments with rabbit mammary cells likewise favour this possibility, and binding of secreted free SC to a specific membrane receptor has been suggested (Kühn & Kraehenbuhl, 1979a). However, it has not been excluded that membrane SC and secreted SC are encoded by two distinct species of messenger RNA, as has recently been reported to be the case for the μ chains of membrane-bound and secreted IgM produced by human lymphoblastoid cell lines (McCune *et al.*, 1980; Singer, Singer & Williamson, 1980). Secondly, although immunoelectron microscopy has indicated that the luminal exteriorization of secretory IgA occurs by opening or extrusion of vesicles (Fig. 2), it is not known how the SC–Ig complexes are released from the membranes of the vesicles to which they are bound (Nagura *et al.*, 1979b). It has to be postulated that SC in some unexplained way is cleaved from the membrane. Thirdly, it has been indicated that the locally produced IgA dimers pass preferentially from the plasma cells to nearby SC-producing glandular cells (Brandtzaeg & Baklien, 1977). The possibility should hence be considered that there is a directional diffusion of locally produced IgA and IgM, in view of recent information that fluid movement in tissue spaces occurs mainly in small rivulets (Guyton, 1976).

Before the answers to these various unsolved aspects are at hand, the proposed transport model has to be considered hypothetical, and further experimental work is required. Critical definition of the individual steps involved in the epithelial transport of dimeric IgA and pentameric IgM is of great general interest since previous knowledge about active transport of macromolecules across biological membranes is meagre. Of more specific immunological interest is the possibility that external transfer of secretory immunoglobulins in the future may be manipulated to the benefit of the patient.

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