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Review

Gap junctions and connexin-mediated communication in the immune system

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Abstract

Gap junctions and connexins are present in the immune system. In haematopoiesis, connexin 43, the most widely distributed gap junction protein, appears to be a key player in the development of progenitor cells and their communication with stromal cells. Connexin 43 is expressed by macrophages, neutrophils and mast cells. Lymphocytes also express connexin 43, and inhibition of gap junction channels in these cells by using highly specific connexin mimetic reagents has profound effects on immunoglobulin secretion and synthesis of cytokines. Lymphocytes and leukocytes also communicate directly in vitro with endothelial cells via gap junctions. Connexins are implicated in inflammatory reactions in a range of tissues. Their involvement in atherosclerotic plaque formation in the vascular system is also a current growth point in research, and could lead to the development of therapeutic interventions.

Keywords: Connexin; Inflammation; Lymphocyte; Endothelium; Leukocyte; Monocyte; Macrophage; Mast cell; Intercellular communication

1. Introduction

Multicellular organisms are characterised by the operation of extensive direct intercellular communication networks that link and balance the metabolic and mechanical activities of the individual functional units. Such networks connecting and co-ordinating attached cells are found not only in compact tissues and organs but also in the various cell types of the immune system comprising the lymphoid organs as well as peripheral lymphocytes migrating through the blood and lymphatic networks (Fig. 1). Direct intercellular communication and strong adhesion are effected by gap junctions (see Evans and Martin for a comprehensive review) [1]. The present article collates information on the distribution and possible roles of gap junctions and the channel building blocks, the connexins, in the various branches of the immune system. Connexins, the proteins assembled into gap junction channels, are tetra-pass membrane proteins that oligomerise into hexameric hemichannels called connexons [2]. These proteins range in size from about 25 to 60 kDa with the main amino acid sequence differences found in the variable-length cytoplasmically oriented carboxyl tail. Over 20 different connexins have been identified in murine and human tissues [1]. After the recruitment of hexameric connexons to the plasma membrane, they carry out two functional options.

In the first, they may operate as unapposed hemichannels. In the second, they dock with partner connexons in neighbouring cells, to form gap junctions that allow direct transfer of molecules and ions up to approximately 1.2 kDa between the cytoplasms of the co-operating cells. Connexins have been detected by a variety of techniques in all nucleated cells, excepting adult striated muscle and sperm. In the present article, we review data demonstrating the widespread distribution of connexins in the component parts of immune system and outline and speculate on some functional implications. We also discuss the evidence pointing to the probable roles of connexin-mediated intercellular signalling by cells of the immune system in inflammation. The distribution and likely roles of gap junctions in the immune system have been addressed in previous reviews [3–5].

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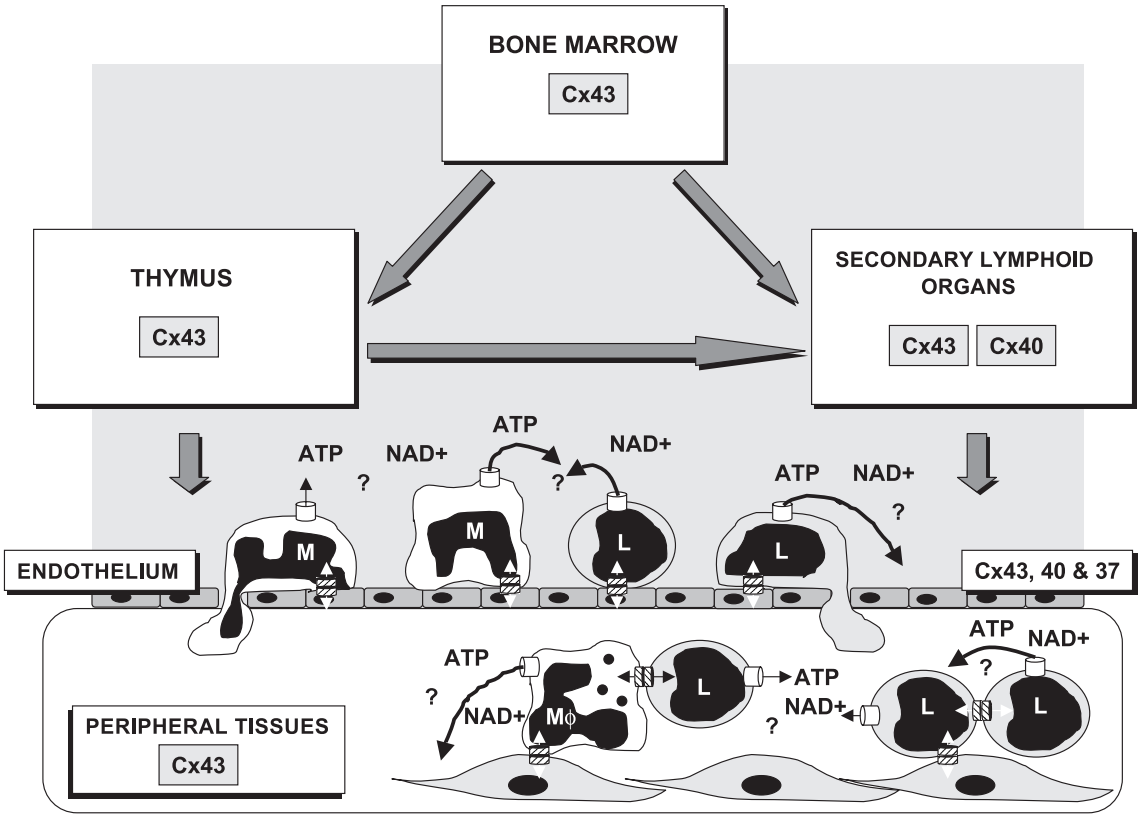

Fig. 1. Diagramatic overview of the distribution of connexins in the immune system. The diagram shows the distribution of connexins in primary, secondary lymphoid organs and the various permutations of connexin-mediated interactions that may operate between monocytes (M) and lymphocytes (L) and endothelium cells of the vascular wall. Monocytes and lymphocytes cross the endothelial and may communicate with it and each other by gap junctions (double barrel) and/or by release of ATP or NAD+ through connexin hemichannels (single barrel). In peripheral tissues, communication via gap junctions or hemichannels by lymphocytes (L) or macrophages (Mϕ) with, for example, stromal cells or fibroblasts may also occur.

In view of the fundamental requirement for the co-operative behaviour of cells comprising the various branches of the immune system (Fig. 1), it is perhaps not surprising that gap junctions and their connexin protein building blocks have been identified in lymphoid tissues and cells (Table 1). Complex homocellular and heterocellular type cross-talk occurring between lymphocytes involves multiple receptor–ligand complexes and ion channels and these cellular interactions, for example, have recently been conceptualised as comprising an immunological synapse [6–9]. Although there is presently no direct evidence showing that connexins reside at such immunological synapses, there is indirect evidence showing that blockage of connexon channel interactions using highly specific peptide reagents disrupts immunoglobulin release and cytokine production by lymphocytes [10]. Furthermore, since cells may express multiple connexins that are likely to be assembled into a permutation of homo/heteromeric connexons, thus providing the basis for homo/heterotypic communication [1,11], these properties can equip cells to fulfil the basic requirements for the extensive and complex cross-talk that characterises the operation of cells in the immune system. Thus, in the various branches of the immune system, connexins and their assembled channels should be considered as components that may complement the complex cascade of molecular interactions that underpin, for example, the rolling of leukocytes on the endothelial wall (Fig. 1), a process involving receptor–ligand interactions that implicate selectins, integrins, sialomucins, etc. [12].

Undoubtedly delaying the growing appreciation of functional roles for connexins in the immune system has been the paucity of morphological evidence for gap junctions in lymphoid organs. This is despite functional evidence for direct communication in cells populating the immune system suggested by the low electrical resistance detected between contacting cells, and especially the direct intercellular transfer between lymphocytes and leukocytes of small highly fluorescent probes.

Nevertheless, the low incidence of morphologically recognised gap junctions and the failure by immunologists to recognise and appreciate the consequences of specific properties highly indicative of direct and rapid intercellular communication in cells of the immune system should not exclude completely the operation of a system that is widespread in almost all tissues and organ systems. It is also worth pointing out at this stage that a connexin-dependent mechanism of intercellular communication that

Table 1
Gap junction intercellular communication and connexin expression in cells of the immune system

Cell type	Morphology	Dye transfer	Connexin (Cx) isoform	References
Homotypic interaction				
T lymphocytes[a]	+	+	Cx43, Cx40	[59]
B lymphocytes[a]	+	+	Cx43, Cx40	[59]
Bone marrow stromal cells (BMSC)	+	+	Cx43	[37, 105–109]
Follicular dendritic cells (FDC)	+	+	Cx43	[42,43, 110]
Thymic epithelial cells (TEC)	+	+	Cx43	[5,38]
Monocytes	+	–	Cx43	[78]
Macrophages	+	–	Cx43, Cx37	[48,82, 111]
Polymorphonuclear neutrophils (PMN)	+	+	Cx43	[54]
Mast cells	+	–	Cx43	[18]
Heterotypic interaction				
T–B cells[a]	+	+	Cx43, Cx40	[59]
T cells–endothelium	+	+	Cx43	[75,110]
T–TEC[b]	+	+	Cx43	[34]
B–FDC	+	+	Cx43	[42,110]
Haematopoietic stem cells–BMSC	+	+	Cx43	[36,37, 112]
FDC–endothelium	+	–	Cx43	[110]
PMN–endothelium	+	+	Cx43	[54,100]
Monocytes–endothelium	+	–	Cx43	[70,78]
Macrophages–endothelium	+	+	Cx43	[70,113]
Macrophages–smooth muscle cells	+	–	Cx43	[70,78, 79,82]
Mast cells–fibroblast	+	–	Cx43, Cx32	[18]

[a] Derived from peripheral blood and/or secondary lymphoid organs.
[b] Thymocytes.

features the propagation of calcium waves between cells featuring unopposed connexin hemichannels in the plasma membrane is now being studied in an increasing number of mammalian cells (Fig. 1). This connexin-dependent mechanism of intercellular communication does not appear to utilise morphologically identifiable gap junctions, and features the release by cells of adenine nucleotides, especially ATP, that induce calcium signalling in close neighbours and implicating plasma membrane purinergic receptors [13–16]. Also this mechanism appears to be sensitive to cellular injury, e.g. in hypoxic conditions. Although the precise mechanism of ATP liberation by cells and the contribution of connexin hemichannels are unclear, the probable involvement of connexin hemichannels in this release process has been highlighted recently by studies showing that short connexin mimetic peptides, which correspond to amino acid sequences in the two extracellular loops of connexin 43, inhibit the release of ATP by cells induced either by photoliberation of intracellular IP_3 or by reducing extracellular calcium levels [17–19]. The connexin mimetic peptides are well-studied inhibitors that prevent Ca^{2+} wave propagation via hemichannels as well as gap junctional communication in tracheal epithelial cells [20,21]. This variation suggests that the inhibitory action of connexin mimetics on connexin hemichannels and gap junctions may vary between different tissues. Connexin hemichannels were predicted to exist on the plasma membrane from gap junction biosynthetic considerations [1,22,23], the penetration into cells of small dyes and the blockage of this dye uptake by cells by connexin antibodies [24] and from electrophysiological approaches [25–28] using *Xenopus* oocytes [29,30] and cells of the retina [31]. Their gating and regulation are being studied [32]. The potential functional importance of these unapposed connexin hemichannels is increasingly being defined in several cell types and these results clearly broaden the scope of intercellular communicative action by plasma membrane channels constructed of connexin subunits.

1.1. Gap junctions and connexins during haematopoesis

Detailed characterisation of connexin expression has been carried out in the haematopoetic system where stem cells have the ability to renew themselves and give rise to the nine or more types of circulating blood cells. Earlier studies showed that connexins 30.3, 31, 31.1, 43, and 45 mRNA are expressed [33] but analysis of freshly isolated bone marrow cells as well as studies in derived cell lines concluded that connexin 43 was by far the major gap junction protein expressed by the specialised microenvironmental stromal cells as well as stem cells (Fig. 1) [33–36]. The regulatory mechanisms operational during haematopoesis are complex [35]. Nevertheless, present evidence strongly points to important roles for connexins and gap junctions in effecting communication between haematopoetic stem cells and stromal cells [35,37]. The generation of Cx43 knockout mice has allowed more definitive studies that have further emphasised the critical role of this connexin in the intercellular networks that operate during haematopoiesis [33,35].

1.2. Gap junctions and connexins in lymphoid organs

T-cell lymphoid progenitors differentiate in the bone marrow and then migrate into the thymus where tight intercellular contact and adhesion with stromal cells contribute to their maturation. The thymus, with its compact meshwork of cells ensuring direct exchange of intercellular information, provides the organ platform where T cell clones differentiate to provide ultimately the peripheral repertoire of circulating cells. Thymic epithelial cells and thymocytes have been shown to form functional gap junction channels in both homotypic and heterotypic modes [38,39]. Again, these gap junctions are constructed exclusively of connexin 43, and many studies have shown that their function is differentially modulated by a variety of soluble factors

including growth hormones [5]. Effector and memory cell clones migrate from primary (thymic) to secondary (lymph node) lymphoid organs where they maturate further and differentiate upon antigen stimulation, a process that is acutely dependent on direct cell-to-cell contact and co-operation. In this crucial differentiation step, other antigen-presenting cells and epithelial supporting cells play important roles. [40,41]. Connexin 43 appears to be the sole connexin expressed in lymphoid tissue (Fig. 1), and supporting its implication in antigen processing and presentation are studies showing that connexin 43 mRNA and protein expression are directly up-regulated by antigenic challenge [42]. Such studies suggest that connexin 43 is highly likely to participate in antigen processing and presentation.

Follicular dendritic cells are also key players in antigen presentation in secondary lymphoid organs with evidence from dye transfer studies for direct communication between each other and with B-lymphocytes implicating connexins [42]. It has been proposed that gap junctions contribute to the development and metabolism of germinal centres by controlling the growth follicular dendritic cells [43].

1.3. Gap junctions in the innate immune system

The innate immune system provides the first line of defence against pathogen infection, and consists mainly of phagocytic cells (neutrophils and macrophages) as well as dendritic and natural killer cells that act in an integrated fashion to eliminate infectious agents [44,45].

A number of studies have pointed to the presence of gap junctions in contacting macrophages [46–48] and between macrophages and intestinal epithelial cells [49], although some of these studies are controversial [48]. Specifically, electron microscopic analysis of bone marrow has shown gap junction-like structures in contacting macrophages and between macrophages and reticular cells, neutrophils, eosinophils, monocytes and erythroblasts [50]. These studies suggest a role for macrophages in haematopoesis. The identification of connexin 43 as the constituent protein of macrophage gap junctions has been confirmed [51–54]. Continuing studies have focussed on the regulation of these gap junctions by a range of pro-inflammatory factors such as cytokines as well as growth factors [51–53]. Connexins have emerged as key proteins in polymorphonuclear neutrophil functions after these cells are activated by lipopolysaccharide in vivo and in vitro [54]. Corroborative studies have identified gap junctions at leukocyte–leukocyte and leukocyte–endothelial cell contacting areas, and gap junctions are implicated in their trans-endothelial migration and its modification under inflammatory conditions [42,51,54,55]. Both connexins 43 and 40 have been detected in these cells [56]. Coupling/attachment of neutrophils to endothelium by gap junctions is a time-dependent process that is modulated by the cytokine tumour necrosis factor and is facilitated by heterotypic cell adhesion involving a range of well-studied adhesion molecules [56].

Mast cells, located in mucosa and connective tissue, account for less than 0.2% of leukocytes, and their proliferation is dependent on direct interactions with T lymphocytes although mastocytes in connective tissue interact extensively with fibroblasts [18]. These cells are major participants in allergic interactions and in providing immunity to parasitic infections. Gap junctions connecting mast cells and fibroblasts were shown by electron microscopy in a chick embryo model [19], and they appear to be constructed of connexins 32 and 43. Such studies strengthen the universal roles played by gap junctions in the physiology of tissue microenvironments, but the effects of reagents that inhibit and disrupt gap junctions in these systems are awaited.

1.4. Connexins and communication in lymphocytes and between lymphocytes and endothelial cells

The pioneering electrophysiological studies of Hulser and Peters [57,58], demonstrating low intercellular resistance properties indicative of the presence of gap junctions linking attached lymphocytes, drew little attention for over 20 years. No doubt, this lack of recognition of a role for connexins in lymphocyte signalling persisted because of the perceived limited requirement for such a mechanism in cells that spend much of their time migrating through the lymphatic and blood vessels. However, several lines of evidence, accrued in many laboratories, have independently corroborated these important early studies.

Peripheral T, B and NK lymphocytes purified from healthy humans express connexin 43. Lymphocytes derived from secondary organs express, in addition, relatively low levels of Cx40 [59]. Flow cytometry approaches using anti-peptide connexin antibodies that bind to the extracellular loops confirmed that the connexins are located on the cell surface (Fig. 2) [59]. These observations are also highly suggestive of the presence of unapposed connexon hemichannels on lymphocytes with independent alternative communication functions such as the ATP-mediated propagation of calcium waves [60–62]. Calcein, a gap junction permeant fluorescent dye, was observed to transfer between contacting lymphocytes; importantly, this direct transfer was inhibited by two categories of gap junction inhibitors [59] and thus implying direct communication across these junctions. 18-α-Glycyrrhetinic acid, a widely used inhibitor of gap junctional communication, is likely to enter cells and modify protein kinases that feature in the regulation of connexin 43 [63,64] that is extensively phosphorylated at multiple serine residues and a few threonine residues on the cytoplasmic tail [65]. In contrast, the connexin mimetic peptides that bind to two specific amino acid regions on the extracellular loops of connexin 43 are unlikely to penetrate into cells, undoubtedly a property accounting for their high specificity and the absence of inhibition of cellular metabolism [66]. Connexin mimetic peptides are thus emerging as useful tools

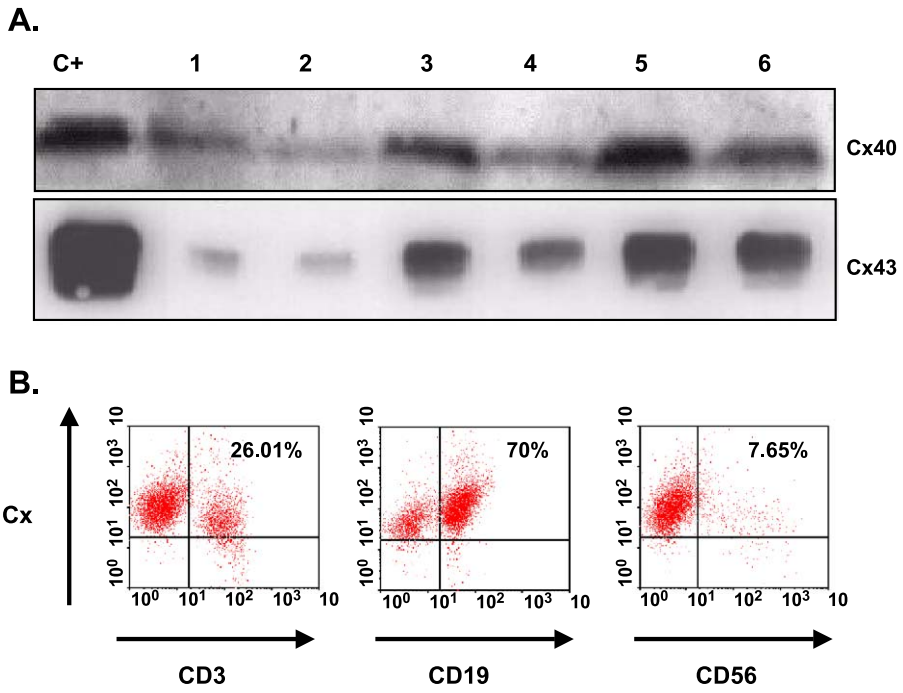

Fig. 2. Connexins 43 and 40 are expressed by cell extracts (A) and at the plasma membrane (B) of T, B and NK human lymphocytes. In A, lymphocytes were treated with phytohaemagglutinin (PHA-L) (lanes 1, 3 and 5) and lipopolysaccharide (LPS) (lanes 2, 4 and 6) for 0, 6 and 12 h, respectively; cellular proteins were separated by SDS-polyacrylamide gel electrophoresis; and connexin expression analysed by Western blotting using antibodies to connexins 43 or 40. Note the increase in connexin expression following addition of the two polyclonal stimulators. In B, cell surface expression of connexins was studied by FACS analysis by double labelling with T cell (anti-CD3), B cell (anti-CD19) and NK cell (anti-CD56) antibodies and a connexin antibody generated to the extracellular loops of connexin 43 [59].

in the functional dissection of gap junctions in the immune system and in unravelling roles for connexon hemichannels in cell–cell signalling [17,61,62]. The adoption of two means of connexin-mediated Ca^{2+} signalling between cells involving both hemichannels and gap junctions and the variable contribution of each route to overall communication is also likely to be influenced by the partner cells and the extracellular matrix as exemplified by the roles of integrins in modulating gap junctional communication in alveolar cells [21,67,68].

Connexin mimetic peptides have emerged as important reagents in revealing roles for connexins as functional players in lymphocytes. Exposure of lymphocytes for 10–50 h to GAP26 and GAP27, short peptides that correspond to specific amino acid sequences in the extracellular loops of connexin 43, markedly reduced the production of immunoglobulins (Ig) G, M and A in mixed cultures of human T and B lymphocytes [10] (Fig. 3). A small degree of intercellular channel rectification was observed in heterotypic and homotypic T and B cell cultures suggesting a role for lymphocyte gap junctions in the polarisation of the immune response [10]. Addition to cell media of connexin mimetics also demonstrated complex temporal inhibitory effects on the synthesis of cytokines, but less so on IL-2 and especially IL-10 (Fig. 3). FACS analysis using extracellular loop antibodies to connexin 43 of lymphocyte populations revealed differences indicating that CD4+, CD8+ and CD19+ cells displayed a characteristic surface patterns under mitogenic stimulation [59].

Interaction between lymphocytes and endothelial cells is a central feature of vascular physiology. Blood-borne lymphocytes leave the circulation via specialised postcapillary vessels, the high endothelial venules (HEV) [12]. The active processes of adhesion and transmigration across the endothelial cell layer are complex and involve a series of time-dependent molecular mechanisms which guarantee not only adhesion but also direct intercellular communication. Gap junctions are present in varying degrees of complexity along the vascular tree [69], and connexin43 [55,70], connexin40 [71,72] and connexin37 [73,74] have been found to be consistently expressed in the vascular wall as determined by mRNA and protein analysis. Lymphocytes establish functional gap junction channels with endothelial cells in vitro during active transendothelial migration in a time-dependent manner; these studies were reinforced by others showing that the process was inhibited by connexin mimetic peptides (Fig. 4) [75].

1.5. Connexins as possible inflammatory response markers

Inflammation is a local or systemic response of a tissue to infection and usually leads to structural or functional damage. Although the overall inflammatory response is

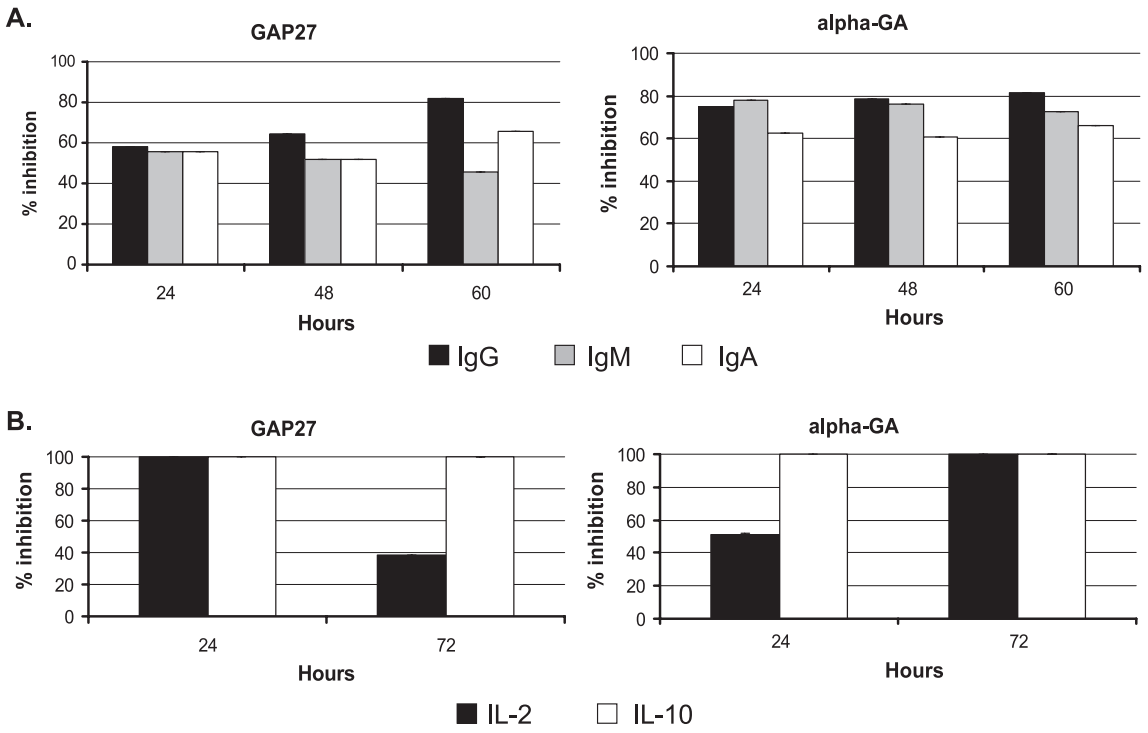

Fig. 3. Gap junction inhibitors decrease production by mixtures of T and B lymphocytes of (A) various immunoglobulins and (B) cytokines. Panel A shows the inhibition of IgG, IgM and IgA by connexin mimetic peptide GAP27 or 18-α-glycyrrhetinic acid (alpha-GA) over 60 h. Panel B shows the inhibition of IL-2 and IL-10 by GAP27 and 18-α-glycyrrhetinic acid over 72 h.

causally diverse, leukocyte migration, activation and maturation are key components. Leukocytes gain access to inflammation sites by interacting with parenchymal cells and the extracellular matrix, and an important aspect of their involvement in inflammation involves transmigration across endothelium.

There is increasing evidence for the implication of connexins, especially connexin 43 during inflammation. Endothelial and smooth muscle cells express connexin 43 with endothelial cells also expressing connexin 37 [1]. Normally, mononuclear cells are rarely found in subendothelial spaces but during tissue or local vascular inflammation, such as in atherosclerosis, there is a large increase in monocyte and lymphocyte numbers that associate with the vascular wall and permeate extensively into the subendothelial spaces [76,77]. In vitro studies have shown that co-culturing endothelial and smooth muscle cells resulted in increased production of IL-1 and IL-6 transforming growth factor, and, importantly in the present context, significantly higher expression of connexin 43 [78]. Connexin 43 expression by leukocytes is also susceptible to LPS stimulation and increased during ischaemia reperfusion injury [54]. These observations combine to suggest a connexin involvement in the overall inflammatory response in the arterial wall. A range of supporting studies, carried out mainly in vitro, have demonstrated that gap junction-mediated communication operates as assessed by direct dye transfer between peripherally derived monocytes and endothelial and smooth muscle cells or between macrophage foam cells [55,79]. Furthermore, lipid loading of monocytes/macrophages markedly reduced gap junctional communication [80]. Expression of connexin 43 is increased in areas of vessel intimal thickening at atheromatous lesions where foam cells aggregate [55,79]. However, a direct functional role specifically for connexin 43 is still controversial and difficult to establish unequivocally since other connexins including connexins 30, 37, and 45 are identified in these lesions [81]. Further supporting the role for connexin 43 in the inflammatory response are recent studies by Kwak et al. [82] who studied expression patterns of connexins 37, 40 and 43 in low-density-lipoprotein-deficient mice and in human atherosclerotic plaques where a redistribution of these connexins in the arterial wall occurred during the development of atheroma [82]. Analysis of the progression of atheroma indicated that it was much reduced in the aorta of low-density-lipoprotein-deficient mice as compared to controls, and these mice exhibited fewer fibrous caps. Furthermore, and of direct clinical relevance, are results showing that statins, drugs that reduce cholesterol synthesis by inhibition of HMG CoA reductase, reduced connexin 43 expression by cultured endothelial cells [83]. These diverse observations strongly indicate that connexin 43 and therefore channels constructed of this protein are implicated in inflammatory events leading to atheroma.

Besides involvement in inflammatory events in the cardiovascular system, connexin expression is modified in inflammatory events in other organ systems. When inflam-

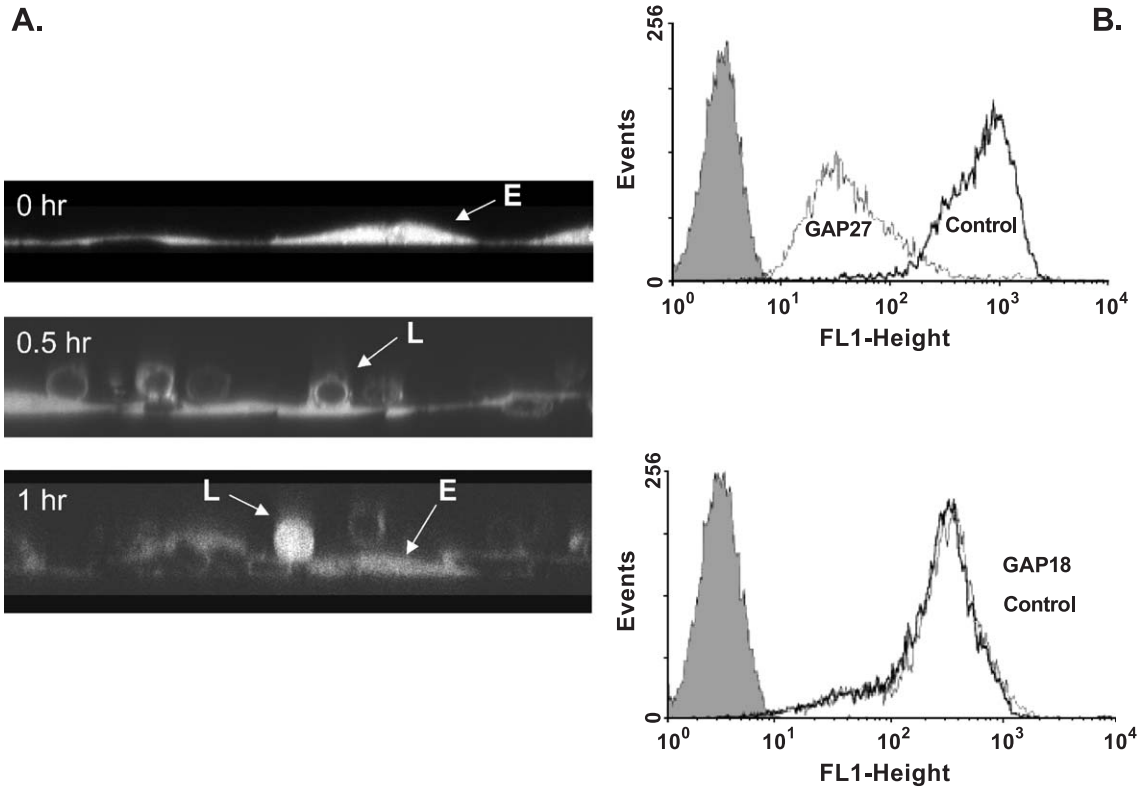

Fig. 4. Direct intercellular communication via gap junctions between lymphocytes and endothelial cells. (A) During transendothelial migration in an in vitro assay, the transfer of calcein (a low molecular weight green fluorescent dye) from endothelial cells (E) to lymphocytes (L) was analysed over time by two photon laser scanning microscopy. In B, the specificity of transfer by a connexin-mediated mechanism was determined by FACS analysis of the dye transfer occurring in the trans-well migration system. Connexin mimetic peptide GAP27 inhibited calcein transfer between endothelial cells and lymphocytes; as a control, GAP18 (a peptide incorporating a short amino acid sequence in the intracellular loop of connexin 43) was used [75].

matory cells invade and damage tubular and interstitial cells in kidneys of patients with glomerulitis, connexin expression increases in parallel with ICAM-1 and VCAM-1 [84,85]. Connexins and gap junctions were also modified when damage occurred in the central and peripheral nervous systems. In the central nervous system, connexins are widely distributed with connexin expression varying during development and in injury processes. In summary, neurons express mainly connexins 32, 36 and 43, oligodendrocytes express connexins 29, 32 and 47, and astrocytes express connexins 26, 30 and 43 [86–90]. Leukocytes have been implicated in cerebral ischemia [91], where a role for connexins and especially connexin hemichannels in astrocytes has been investigated in stroke models [92]. In peripheral nerves, connexin 43 is mainly associated with perineural fibroblasts and Schwann cell cytoplasm [93–95], and there is high expression of connexin 32 at reflexive gap junctions in Schwann cells [96].

Connexin expression is modified in the inflammatory response to peripheral nerve damage and this has been investigated in mouse and rat models of sciatic nerve damage [97–99]. After injury there are changes in connexin 32 and 46 expression. Interestingly, there appears to be a linkage between the down regulation of connexin 32 and up-regulation of connexin 43 in endoneural fibroblasts and infiltrating macrophages. It has been proposed that many of these changes in various cell types are induced by the release of inflammatory cytokines by endothelial cells and transmigrating leukocytes [78,100]. The changes in expression of connexins 32 and 43 appear to vary according to the tissues examined. In liver, for example after LPS induced inflammation, connexin 32 is rapidly degraded [101–103], an event that coincides with a decrease in cell communication ascertained by lowered dye coupling [104].

Connexin 26 is one of the smallest connexins with a short 16-amino-acid cytoplasmic tail (connexin 43 has a tail of 156 amino acids). Connexin 26 is associated with inflammation in the cochlea where cells of the stria vascularis are connected by gap junctions. It has been suggested that local release of proinflammatory cytokines such as tumour necrosis factor alpha or interleukin 1 beta by immune system cells may contribute to the lowering of connexin 26 expression. This decrease in connexin 26 levels in the ear contrasts with the lack of change in connexin 26 expression in liver following LPS treatment [104].

The above observations combine to indicate that acute inflammation involving cells of the immune system can trigger changes in the expression and probably the functional involvement of gap junctions communication chan-

nels in a number of tissue/organ systems infiltrated by leukocytes.

However, it is apparent that these changes monitored at the protein or RNA levels are complex and vary between various tissue/organ systems. However, one may generalise and comment that changes in connexin 43 are mainly associated with early inflammatory events involving macrophage infiltration and endothelial cell activation. In contrast, down-regulation of connexin 32 seems to point to tissue damage and the consequential functional disruption. Various systems are thus likely to be affected in different ways probably because of the presence of different connexin expression profiles allowing channels linking similar and dissimilar cells with varying selectivity to be established.

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