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Connexins and their channels in inflammation

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Abstract

Inflammation may be caused by a variety of factors and is a hallmark of a plethora of acute and chronic diseases. The purpose of inflammation is to eliminate the initial cell injury trigger, to clear out dead cells from damaged tissue and to initiate tissue regeneration. Despite the wealth of knowledge regarding the involvement of cellular communication in inflammation, studies on the role of connexin-based channels in this process have only begun to emerge in the last few years. In this paper, a state-of-the-art overview of the effects of inflammation on connexin signaling is provided. *Vice versa*, the involvement of connexins and their channels in inflammation will be discussed by relying on studies that use a variety of experimental tools, such as genetically modified animals, small interfering RNA and connexin-based channel blockers. A better understanding of the importance of connexin signaling in inflammation may open up towards clinical perspectives.

Keywords

Connexins; gap junctions; hemichannels; inflammation; cytokines

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1 Introduction

In multicellular organisms, homeostasis is controlled by 3 communication mechanisms acting at the intracellular, extracellular and intercellular level. The latter is mainly mediated by gap junctions (GJs) (Su and Lau, 2014), which appear as plaques at the cell plasma membrane surface and are formed by the interaction of 2 hemichannels (HCs), one contributed by each of the adjacent cells (Vinken *et al.*, 2006, Vinken *et al.*, 2011). Each HC is composed of 6 connexins (Cxs), which are transmembrane (TM) proteins consisting of a cytoplasmic loop (CL), 2 extracellular loops (EL), a cytoplasmic *C*-terminal tail and a cytoplasmic *N*-terminal tail (Vinken *et al.*, 2012, Maes *et al.*, 2014). More than 20 different Cx species have been identified in human and they are all named after their predicted molecular weight, expressed in kilodaltons. GJs allow the intercellular transfer of small and hydrophilic molecules with a molecular weight below 1-1.5 kilodalton, such as adenosine triphosphate (ATP), inositol triphosphate and cyclic adenosine monophosphate, as well as ions. This flux is called gap junctional intercellular communication (GJIC) (Decrock *et al.*, 2009, Chandrasekhar and Bera, 2012, Wang *et al.*, 2013b). The latter can be regulated by different mechanisms including pH, transmembrane voltage and calcium concentration (Cottrell and Burt, 2005). Posttranslational modifications, such as S-nitrosylation, sumoylation and phosphorylation, also directly regulate gap junction opening (Johnstone *et al.*, 2012). Upon degradation, gap junctional channels are internalized by one of the 2 opposing cells, resulting in the formation of an annular gap junction. These structures are further degraded by both lysosomes and proteasomes (Laird, 2005, Laird, 2006). When unopposed, HCs have the potential to form a transmembrane conduit between the cytosol of an individual cell and its extracellular environment, and to convey a number of critical molecules, including ATP, nicotinamide adenine dinucleotide, glutamate and prostaglandins (Figure 1) (Wang *et al.*, 2013b). While GJs are usually open in physiological conditions, HCs are typically closed yet can be activated by a number of pathological triggers, such as increases membrane depolarization, increases in intracellular calcium (De Vuyst *et al.*, 2006, Wang *et al.*, 2013a) or decrease in extracellular calcium concentration (Srinivas *et al.*, 2006), mechanical stimulation (Luckprom *et al.*, 2011), changes in Cx phosphorylation status (Alstrom *et al.*, 2015), oxidative stress (Riquelme and Jiang, 2013), ischemia/reperfusion insults (Wang *et al.*, 2013c) and inflammatory conditions (Takeuchi and Suzumura, 2014, Calder *et al.*, 2015). Cx proteins can also affect cellular functions independently of their channel-forming properties by altering the expression of homeostasis determinants or by direct interaction with cell growth and cell death regulators through binding of cytoplasmic proteins to the *C*-terminal tail (Vinken *et al.*, 2012, De Bock *et al.*, 2015).

Interesting experimental and therapeutic tools are the peptide inhibitors of connexin-based channels, especially those who mimic specific connexin sequences. In contrast to carbenoxolone, a typical inhibitor of GJs and connexin-based HC's, these mimetic peptides have better selectivity. Over the past ten years, several peptides have been demonstrated to block hemichannels, including Gap26, a peptide identical to a sequence on the first EL of Cx43 (Wang *et al.*, 2013a), Gap27, a peptide identical to a sequence on the second EL of Cx37 and Cx43 (De Bock *et al.*, 2011), Peptide5, a Cx43 HC-blocking mimetic peptide

(Danesh-Meyer *et al.*, 2012) and Gap19, a synthetic nonapeptide that mimics a sequence in the cytoplasmic loop area of Cx43 (Wang *et al.*, 2013a).

Inflammation is a first-line mechanism in the innate immune response in order to protect the organism against pathogens and deleterious effects of cell damage. This complex process encompasses a multistep reaction, involving recruitment of immune cells, vasodilatation, increased permeability and an extensive set of molecular mediators. Its goal is to eliminate the initial cause of cell injury, clear out necrotic cells damaged upon the insult and to initiate tissue repair (Toskala, 2014, Shalapour and Karin, 2015, Waisman *et al.*, 2015). Both microbiologically-induced inflammation and sterile inflammation are characterized by the recruitment of neutrophils and macrophages as well as by the production of inflammatory cytokines and chemokines (Chen and Nuñez, 2010). In particular, Toll-like receptors are expressed on various immune cells, such as macrophages, dendritic cells, B-cells and neutrophils, and on non-immune cells in brain, heart, intestine, lung, liver and kidney (Kawai and Akira, 2007, Vaure and Liu, 2014). Toll-like receptors constitute a family of primary sensors that detect damage-associated molecular patterns (DAMPs) (Chen and Nuñez, 2010), released by damaged cells, or pathogen-associated molecular patterns (PAMPs), like peptidoglycan from most bacteria and lipopolysaccharide (LPS) from Gram-negative bacteria (Akira *et al.*, 2006, Kawai and Akira, 2007, Lu *et al.*, 2008). Toll-like receptor activation occurs through receptor dimerization, which requires cluster of differentiation 14 and myeloid differentiation factor 2. Subsequently, the transcription factor nuclear factor (NF) κ-light-chain-enhancer of activated B cells κB, present in the cytosol under basal conditions, becomes activated and transported to the nucleus. At this location, NF-κB regulates the expression of cytokines, cyclo-oxygenase 2, growth factors and inhibitors of apoptosis and the expression of pro-interleukin (IL)-1β, which is then cleaved in the cytosol by caspase 1 to active IL-1β (Figure 2). Finally, the latter is released in the extracellular environment and can induce the production of an array of pro-inflammatory mediators, such as IL-6, tumor necrosis factor (TNF)-α and nitric oxide synthase (NOS), leading to NO formation (Lucas and Maes, 2013).

In the last decade, it has become clear that the inflammatory response relies, at least in part, on cellular communication mediated by Cx proteins and their channels (Tables 2 and 3) (Chanson *et al.*, 2005, Brisset *et al.*, 2009, Morel *et al.*, 2009, Scheckenbach *et al.*, 2011, Maes *et al.*, 2015b, Meens *et al.*, 2015). This paper will give an overview of these aspects in different organs.

2 Connexin signaling and inflammation

2.1 Brain and spinal cord

2.1.1 Effects of inflammation on connexins and their channels in the brain and spinal cord—

The brain is a highly differentiated, heterogeneous and complex organ that requires various control mechanisms, including cellular communication through Cx-based channels (Table 1) (Scheckenbach *et al.*, 2011). In the brain, Cx43 is most prominently produced by astrocytes, while microglial cells mainly harbor Cx32 and Cx26 (Giaume and Theis, 2010, Takeuchi and Suzumura, 2014). A number of other Cxs, including Cx26, Cx30, Cx40, Cx45 and Cx46, have been detected in astrocytes *in vitro* (Kunzelmann

et al., 1997, Dermietzel *et al.*, 2000). Brain oligodendrocytes express Cx32, Cx47 and Cx29, whereas neurons produce Cx36 and Cx45 (Moore and O'Brien, 2015). The blood-brain barrier is a selective permeability barrier that separates circulating blood from the brain extracellular fluid. The blood-brain barrier is formed by endothelial cells and pericytes, which express Cx37, Cx40 and Cx43, as well as by astrocytes that express Cx43, Cx30 and Cx26 in decreasing order (Traub *et al.*, 1998, Nagasawa *et al.*, 2006, De Bock *et al.*, 2014). In the spinal cord, developing motor neurons show expression of Cx36, Cx37, Cx40, Cx43, and Cx45 mRNA (Tonkin *et al.*, 2014). Spinal astrocytes contain Cx30 and Cx43, and spinal oligodendrocytes stain positive for Cx29, Cx32 and Cx47.

Upon peripheral injury, pro-inflammatory cytokines are released into the blood circulation and attract leukocytes (Chanson *et al.*, 2005). These cytokines make the blood-brain barrier more permeable, resulting in the invasion of blood cells into the central nervous system and hence the occurrence of neuro-inflammation (Takeuchi and Suzumura, 2014). In Rasmussen encephalitis, a rare condition characterized by sustained brain inflammation, epilepsy and progressive cognitive deterioration in children, expression of Cx32 in brain tissue is decreased, while Cx26 production remains unchanged. Interestingly, GJ coupling in cortical pyramidal neurons in brain tissue from Rasmussen encephalitis patients is enhanced (Cepeda *et al.*, 2015). Demyelination, being the loss of myelin surrounding the nerves, is a hallmark of some neurodegenerative auto-immune diseases, including multiple sclerosis, encephalomyelitis and chronic inflammatory demyelinating polyneuropathy. As such, inflammation may drive demyelination associated with such diseases through overproduction of cytokines *via* upregulation of TNF-α (Ledeen and Chakraborty, 1998). In this regard, Cx32-based and Cx47-based GJ formation in oligodendrocytes is compromised within lesions in multiple sclerosis patients, while Cx30 and Cx43 levels are augmented as part of astrogliosis (Markoullis *et al.*, 2012b, Lieury *et al.*, 2014, Markoullis *et al.*, 2014). Moreover, Cx32 production is downregulated along myelinated fibers, yet Cx47 shows enhanced expression mainly in oligodendrocyte precursor cells (Markoullis *et al.*, 2012b). Similar changes in Cx expression patterns are observed in an experimental model of auto-immune encephalomyelitis in mouse (Markoullis *et al.*, 2012a). LPS injection in rats shows that activation of apoptosis in oligodendrocytes is an early event in demyelination concomitant with loss of Cx43 in the *corpus callosum* (Zhang *et al.*, 2013a). Astrocytes are of importance in initiating and regulating the release of pro-inflammatory cytokines, including IL-1β and TNF-α (Dong and Benveniste, 2001, Farina *et al.*, 2007). On their turn, IL-1β and TNF-α underlie the regulation of GJs and HCs in astrocytes. Overall, they reduce GJIC and open HCs (Orellana *et al.*, 2009, Abudara *et al.*, 2015). In fact, the former is disadvantageous for neurons as their survival heavily relies on cellular communication with astrocytes. Consequently, astrocytes can be considered as key players in infectious and neurodegenerative diseases in the central nervous system (Kielian, 2008, Quintanilla *et al.*, 2012). Intracerebroventricular injection of LPS in rats upregulates Cx32 mRNA levels and decreases Cx43 expression in the hippocampus (Abbasian *et al.*, 2012, Sayyah *et al.*, 2012, Abbasian *et al.*, 2013). When exposed to inflammatory agents, including cytokines, LPS and amyloid-β, astrocytes exhibit deterioration of GJIC (De Vuyst *et al.*, 2007, Cruz *et al.*, 2010, Hinkerohe *et al.*, 2010, Liao *et al.*, 2010, Orellana *et al.*, 2010, Fruscione *et al.*, 2011), but increased HC activity (Retamal *et al.*, 2007, Orellana *et al.*, 2010, Orellana *et al.*, 2011). In

this respect, IL-1β inhibits GJ coupling and GJ conductance, along with a drop in Cx43 protein and mRNA expression in primary human fetal astrocytes (John *et al.*, 1999, Duffy *et al.*, 2000). Similarly, TNF-α treatment of primary rat astrocytes results in GJIC inhibition with simultaneous phosphorylation of Cx43 (Haghikia *et al.*, 2008b). NO is a mediator of inflammation by influencing phagocytes, leukocyte adhesion and smooth muscle cell dilation. As such, exposure of astrocytes to LPS leads to a dramatic augmentation of NOS (Liao *et al.*, 2010), thereby catalyzing the production of NO, and to a dose-dependent suppression of GJIC (Bolaños and Medina, 1996). This goes hand in hand with decreased Cx43 protein (Haghikia *et al.*, 2008a, Hinkerohe *et al.*, 2010) and mRNA expression (Liao *et al.*, 2010).

Production of pro-inflammatory mediators, like TNF-α, IL-1β and NO, is initiated upon exposure of astrocytes and microglia to *Staphylococcus aureus*, a Gram-positive bacterium able to cause inflammation in the brain. Recognition of peptidoglycan, the major cell wall product of *S. aureus*, in astrocytes and microglia occurs through Toll-like receptor 2 (Esen *et al.*, 2004). Activation of the latter influences the p38 mitogen-activated protein kinase pathway, which in turn reduces Cx43 mRNA and protein expression and abrogates GJIC (Zvalova *et al.*, 2004, Esen *et al.*, 2007). In contrast, upregulated Cx43 mRNA and protein levels are detected in primary microglia (Garg *et al.*, 2005). *Trypanosoma cruzi* and *Toxoplasma gondii*, both zoonotic protozoan parasites able to invade the central nervous system, cause loss of GJIC in astrocytes and leptomeningeal cells without affecting Cx43 expression or its posttranslational processing (Campos de Carvalho *et al.*, 1998, Kielian, 2008). Additionally, human immunodeficiency virus infection of astrocytes results in opening of Cx43-based HCs and triggers a slight reduction in astrocytic GJ coupling (Orellana *et al.*, 2014).

HCs at the blood-brain barrier have been linked to inflammation. In endothelial cells, dye uptake through HCs is induced when immortalized rat brain cells are exposed to conditioned medium harvested from LPS-activated microglia (Orellana *et al.*, 2009). Treatment of immortalized mouse endothelial cells with peptidoglycan, isolated from *S. epidermidis,* also activates Cx43-based HCs. This induces the release of ATP and results in the increased expression of Toll-like receptor 2, thereby potentiating the production of IL-6 (Robertson *et al.*, 2010). Moreover, the inflammatory stressor bradykinin induces HC-mediated calcium oscillations in microvascular brain endothelial cells and subsequent blood-brain barrier disruption (De Bock *et al.*, 2011). The endothelial cytoplasmic calcium concentration plays an important role in blood-brain barrier function, whereby an increase is associated with a dysfunctional barrier (De Bock *et al.*, 2013). After ischemia, HC opening results in an inability for endothelial cells to osmoregulate resulting in vessel leak within 2 hours and microvascular disorganization. Systemic delivery of Peptide5, reduced vascular leak (Danesh-Meyer *et al.*, 2012).

Following spinal cord injury in rats, accompanied by hemorrhage, damage and inflammation (Norenberg *et al.*, 2004), Cx43 protein and mRNA quantities are increased in astrocytes with no changes in the expression of Cx32 and Cx36 (Lee *et al.*, 2005). Fibroblast growth factor (FGF)-1, which is released in spinal cord injury, activates spinal astrocytes in culture leading to cell permeabilization, as evidenced by increased extracellular secretion of ATP and

cytosolic uptake of fluorescent tracers. As shown by the use of ATPase apyrase and by P2X7 receptor antagonists, the compromised cell membrane integrity is mediated, at least in part, by Cx43-based HCs (Garré *et al.*, 2010). In summary, interesting changes in Cx expression are observed in virtually all forms of inflammation related to the brain or spinal cord. Such changes may ameliorate or worsen outcomes of disease.

2.1.2 Roles of connexins and their channels in inflammation in the brain and spinal cord—

Auto-immune encephalomyelitis experimentally evoked in $Cx32^{-/-}$ mice results in an exacerbated clinical course with more pronounced demyelination and axonal loss despite a similar degree of inflammation and an overall milder loss of Cx47-based and Cx43-based GJs (Markoullis *et al.*, 2012a). However, the susceptibility or severity of experimental auto-immune encephalomyelitis does not alter in astrocyte-specific $Cx43^{fl/fl}Cx30^{-/-}$ mice (Lutz *et al.*, 2012). Treatment of astrocytes with a pro-inflammatory cytokine mixture consisting of TNF-α and IL-1β stimulates Cx43-based HC activity (Froger *et al.*, 2010). Interestingly, application of Gap26 and Gap27 or synthetic cannabinoid prevents cytokine-induced neurotoxicity. This demonstrates that inflammation-induced astroglial HC activation fulfills a critical function in neuronal death and suggests a neuroprotective role of Cx43-based blockade. This is substantiated by reduction in Cx43 expression upon treatment of spinal astrocytes with TNF-α and interferon (IFN)-γ, which can be prevented by blocking c-jun terminal kinase (Zhang *et al.*, 2013b) or ubiquitin-proteasome (Zhang *et al.*, 2015), both involved in apoptosis, neurodegeneration and cytokine production. Cx43 HCs play a major role in brain inflammation (Kim *et al.*, 2016), and delivery of Cx43 HC-blocking peptides (O'Carroll *et al.*, 2008) into the ventricles of the brain after ischemia in near-term sheep, a model for cerebral palsy, improves functional elektroretinography outcomes, reduces seizure and status epilepticus, give faster return to normal sleep cycling and promotes both oligodendrocyte and neuronal survival (Davidson *et al.*, 2012). A similar result was obtained in a preterm sheep asphyxia study (Davidson *et al.*, 2014). A recent study using astrocytic-specific $Cx43^{fl/fl}$ mice reveals a decline in ATP-induced inflammation, less manifested macrophage and microglia recruitment, and enhanced functional recovery following spinal cord injury (Huang *et al.*, 2012). Spinal cord of rats treated with Cx43-antisense oligonucleotides or Cx43 HC-blocking mimetic peptides show reduced swelling, inflammation and tissue disruption after injury (Cronin *et al.*, 2008, O'Carroll *et al.*, 2013). Cytoplasmic calcium concentration is an important factor for determining the functional state of the blood-brain barrier. Bradykinin can trigger intracellular calcium oscillations in immortalized and primary brain endothelial cells. These effects are inhibited by blocking Cx-based channels using carbenoxolone, small interfering RNA-based silencing of endothelial Cx37 and Cx43, and Gap27 (De Bock *et al.*, 2011).

2.2 Heart

2.2.1 Effects of inflammation on connexins and their channels in heart—

The predominant Cx species in cardiac tissue are Cx40, Cx43 and Cx45 (Table 1) (Delmar and Makita, 2012, Meens *et al.*, 2015). Cx40 can be found in atrial myocytes, the atrioventricular node, the His-bundle and ventricular conduction system (Gros and Jongsma, 1996, Severs *et al.*, 2004). Cx45 is mainly localized in the sinoatrial and atrioventricular nodes (Jansen *et al.*, 2010) and at the interface between the fast conducting pathway and the working

myocardium (Coppen *et al.*, 1998), while Cx43 is most abundantly present in atrial and ventricular myocytes (Lampe and Lau, 2004, Michela *et al.*, 2015). Most ventricular GJs composed of Cx43 gather at intercalated discs (Vozzi *et al.*, 1999), often with larger junctional plaques at the disc periphery, and are rarely distributed to the lateral membranes of cardiomyocytes. The specific localization of Cx43 is essential for rapid propagation of action potentials (Del Ry *et al.*, 2015, Michela *et al.*, 2015). Emerging evidence has suggested novel roles of Cx43-based HCs in cardiac homeostasis, as unopposed HCs reside in the periphery of GJ plaques termed perinexus (Rhett and Gourdie, 2012). In contrast to GJIC, Cx43-based HCs between the cytosol and the extracellular area of cardiomyocytes may, when open, lead to swelling, cell dysfunction and cell death (Plotkin *et al.*, 2002, Goodenough and Paul, 2003, Wang *et al.*, 2013c). Cx43 mRNA levels are found to be dramatically and rapidly downregulated in rat heart after injection of LPS. Of note, TNF-α decreases Cx43 gene promoter activity in H9c2 myoblast cells (Fernandez-Cobo *et al.*, 1999). Expression of transforming growth factor (TGF)-β, driving cell growth, cell differentiation, apoptosis and cellular homeostasis, is increased during *T. cruzi* infection and regulates fibrosis and the parasite cell cycle. Exposure to TGF-β induces disorganized GJ formation in non-infected cardiomyocytes, accompanied by punctate, diffuse and non-uniform Cx43 staining (Waghabi *et al.*, 2009). Analogous experiments have been performed with infected patients and confirmed downregulation of Cx43 expression, altered distribution of cardiac GJ plaques and a significant reduction in the number and length of Cx43-positive GJ plaques inversely correlating with cardiomegaly and sepsis (Celes *et al.*, 2007, Adesse *et al.*, 2008, Waghabi *et al.*, 2009, Carvalho *et al.*, 2012).

2.2.2 Roles of connexins and their channels in inflammation in heart—In a recent set of studies, lipoxin A4, a bioactive product derived from arachidonic acid and a resolver of inflammation, showed protection of several organs against ischemia/reperfusion insults (Ye *et al.*, 2011, Scully *et al.*, 2012). In ischemia/reperfusion injury in rat, lowered levels of inflammatory cytokines, including IL-1β, IL-6, IL-8 and TNF-α, oxidative stress as well as increased quantities of Cx43 are measured after treatment with lipoxin A4. Moreover, lipoxin A4 preconditioning and postconditioning in myocardial ischemia/reperfusion injury can attenuate metabolic disturbance in myocardium through upregulation of sodium/potassium ATPase expression, an important mediator in the maintenance of cardiac homeostasis (Zhao *et al.*, 2013). Gap19 has been demonstrated to specifically inhibit Cx43-based HCs without affecting its corresponding GJs in cardiomyocytes (Wang *et al.*, 2013c). Importantly, this peptide prevents metabolic inhibition-enhanced HC opening, protects cardiomyocytes against volume overload and cell death following ischemia/reperfusion *in vitro*, and modestly decreases the infarct size after myocardial ischemia/reperfusion in mouse (Wang *et al.*, 2013c). Murine macrophages co-cultured with murine atrial myocyte-derived cells and subjected to mechanical stretch show macrophage migration and transient increases in extracellular ATP concentration. These effects are blocked by the GJ and HC-blocker carbenoxolone and the non-specific ATP signaling modifiers apyrase and pyridoxal-phosphate-6-azophenyl-2',4'-disulfonate (Oishi *et al.*, 2012). This outcome can be reversed if cells are incubated with SB-431542, an inhibitor of TGF-β receptor type I.

2.3 Blood vessels

2.3.1 Effects of inflammation on connexins and their channels in blood vessels—

Cx37, Cx40, Cx43 and Cx45 are expressed in the vascular wall. Cx43, Cx37 and Cx40 are present in endothelial cells, of which their expression levels depend on the type of vessel and its position in the vascular tree (Meens *et al.*, 2015). Cx43, Cx45, Cx37 and Cx40 can be found in smooth muscle cells (Table 1) (Scheckenbach *et al.*, 2011). Lymphatic endothelial cells express Cx37, Cx43 and Cx47 (Meens *et al.*, 2014). In all vascular cells, Cx proteins and their channels play an important role in the coordination of vascular responses. They drive the dynamic modulation of vascular resistance and blood flow to match different tissue oxygen requirements (Schmidt *et al.*, 2008, Johnstone *et al.*, 2009). Moreover, they participate in the development of lymphatic valves (Kanady *et al.*, 2011, Sabine *et al.*, 2012). Consequently, Cx proteins have also been described to be involved in pathological conditions of blood vessels, such as atherosclerosis (Pfenniger *et al.*, 2013). The latter is a progressive disease characterized by the accumulation of macrophages, lymphocytes, smooth muscle cells and lipids in the vascular wall, and is tightly associated with inflammation. Cx37 is expressed in macrophage foam cells and monocytes, which are important mediators in the progression of atherosclerosis. ATP release through Cx37-based HCs is linked to inhibition of leukocyte adhesion, suggesting that these channels may control initiation of atherosclerotic plaque development (Wong *et al.*, 2006). Both Cx37 and Cx40 productions are decreased in the endothelium of atherosclerotic plaques (Kwak *et al.*, 2002, Yeh *et al.*, 2003) and their expression is altered by oxidative stress, prothrombotic molecules and pro-inflammatory agents (Simon *et al.*, 2004, Hou *et al.*, 2008). This is supported by complete disappearance of Cx37 and Cx40 when human umbilical vein endothelial cells are stimulated with TNF-α (van Rijen *et al.*, 1998). Furthermore, Cx43 expression is upregulated in experimental coronary atherosclerosis, especially in macrophage foam cells (Blackburn *et al.*, 1995, Polacek *et al.*, 1997, Kwak *et al.*, 2002). Moreover, LPS-injected rats show enhanced Cx40 expression in the aorta with simultaneous increased levels of inflammatory markers, like C-reactive protein, and oxidative stress markers, including malondialdehyde. Omega-3 fatty acids negatively affect the expression of Cx40 in aortic tissue and suppress C-reactive protein and malondialdehyde production (Frimmel *et al.*, 2014). LPS activates c-jun terminal kinases 1 and 2, p38 and extracellular signal-regulated kinases 1 and 2, yet it also abrogates GJ coupling in endothelial cells isolated from wild-type, $Cx37^{-/-}$ and $Cx43^{G60S}$ mutant mice (Bolon *et al.*, 2007). Although the effects of inflammation on Cx expression and function may differ according to the vascular bed involved, treatment strategies targeting Cxs may improve disease outcome.

2.3.2 Roles of connexins and their channels in inflammation in blood vessels—

Cx37 seems to protect against atherosclerosis since deletion of Cx37 accelerates atherogenesis in $Cx37^{-/-}$/apolipoproteinE$^{-/-}$ mice. These animals show an increase in aortic lesions caused by enhanced monocyte and macrophage recruitment (Wong *et al.*, 2006). Shear stress, an essential feature of atherogenesis (Kwak *et al.*, 2014), applied to the same mouse model is found to increase the atherosclerotic plaque size in $Cx37^{-/-}$/apolipoproteinE$^{-/-}$ animals in comparison with apolipoproteinE$^{-/-}$ counterparts (Pfenniger *et al.*, 2015). When $Cx37^{-/-}$ monocytes or macrophages are introduced in hypercholesterolemic $Cx37^{+/+}$ mice, a higher amount of leukocytes is found in the atherosclerotic plaque,

suggesting a role of Cx37 in monocyte and macrophage function (Wong *et al.*, 2006). Conversely, a polymorphism of Cx37 or blockage of Cx37-based HCs reduces the release of ATP out of the cells and increases their adhesion to substrates (Chanson and Kwak, 2007). Endothelial-specific $Cx40^{-/-}$ mice show spontaneous atherosclerotic lesions in the aorta by promoting leukocyte adhesion through cluster of differentiation 73 (Chadjichristos *et al.*, 2010). The latter fulfills enzymatic activities through the conversion of ATP to adenosine monophosphate and adenosine in immune cells (Chadjichristos *et al.*, 2010, Antonioli *et al.*, 2013). In contrast to the seemingly protective effects of Cx37 and Cx40, Cx43 rather acts in an atherogenic way. Indeed, low density lipoprotein $receptor^{-/-}/Cx43^{+/-}$ mice fed a cholesterol-rich diet display reduced atherosclerosis in the thoraco-abdominal aorta and in the aortic roots in comparison with low density lipoprotein receptor-deficient mice. Specifically, smaller atherosclerotic plaques, fewer inflammatory cells and thicker fibrous caps are found (Kwak *et al.*, 2003, Wong *et al.*, 2003). Targeting the Cx43 microtubule-binding domain by JM2, a Cx43 mimetic peptide identical to a sequence of the *C*-terminal intracellular loop, results in a decrease in ATP release in cultured human endothelial cells and decreases the total inflammatory infiltrate in a rat model of inflammation (Calder *et al.*, 2015), illustrating that targeting endothelial Cx43 might be a promising anti-inflammatory approach.

2.4 Liver

2.4.1 Effects of inflammation on connexins and their channels in liver—

In liver, Cx32 and Cx26 are expressed by hepatocytes (Kyoi *et al.*, 1992, Ohkusa *et al.*, 1995, Iwata *et al.*, 1998, Radebold *et al.*, 2001). Non-parenchymal livers cells, including Kupffer cells, sinusoidal endothelial cells and stellate cells, produce Cx26 and Cx43 (González *et al.*, 2002, Eugenín *et al.*, 2007, Hernández-Guerra *et al.*, 2014). GJIC underlies critical hepatic functions, including xenobiotic biotransformation and plasma protein synthesis (Maes *et al.*, 2015b).

Upon injection of LPS in rodents, decreased Cx32 and Cx26 protein levels at the plasma membrane of hepatocytes are observed. This is reminiscent of what is observed in hepatitis patients in clinical settings (Correa *et al.*, 2004). Additionally, Cx32 mRNA levels are diminished during the inflammatory response in liver, while Cx26 mRNA remains unchanged (De Maio *et al.*, 2000). In primary hepatocyte cultures, IL-1β decreases Cx32 levels and GJIC becomes compromised by TNF-α, IL-1β and IL-6. Hepatic Cx26 mRNA is upregulated after exposure of cultured immortalized hepatocytes to IL-1, IL-6 and TNF-α (Temme *et al.*, 1998). The same holds true for Cx43 protein and mRNA in primary stellate cells exposed to LPS or IL-1β (Fischer *et al.*, 2005). When treated with LPS and IFN-γ, Kupffer cells increasingly express Cx43 *in vitro* and *in vivo* (Eugenín *et al.*, 2007). Moreover, GJIC deteriorates in mice upon intoxication with acetaminophen, which triggers an inflammatory response, and is associated with a switch in mRNA and protein production from Cx32 and Cx26 to Cx43. The upregulation of Cx43 expression is due, at least in part, to *de novo* production by hepatocytes (Maes *et al.*, 2016a). Likewise, Cx32 production is drastically downregulated upon acute-on-chronic liver failure in rats. At the same time, Cx43-positive spots appear in particular in the vicinity of inflamed areas (Balasubramaniyan *et al.*, 2013).

2.4.2 Roles of connexins and their channels in inflammation in liver—

Cx32 exerts a protective effect in experimental non-alcoholic steatohepatitis, a chronic liver disease associated with fat accumulation and inflammation (Willebrords *et al.*, 2015), as based upon increased levels of inflammatory cytokines and more pronounced oxidative stress in Cx32 dominant negative transgenic (Cx32ΔTg) rats (Sagawa *et al.*, 2015). The role of Cx32 in liver injury is further investigated in $Cx32^{-/-}$ mice and Cx32ΔTg rats treated with acetaminophen. Both amplification and alleviation of this toxicological process by Cx32 is described (Naiki-Ito *et al.*, 2010, Igarashi *et al.*, 2014, Maes *et al.*, 2016b). Acetaminophen causes liver damage, inflammation and oxidative stress upon overdose. However, $Cx32^{-/-}$ mice display no differences in inflammation, cell death and oxidative stress in comparison with wild-type mice (Maes *et al.*, 2016b). $Cx43^{+/-}$ mice tend to show increased liver cell death, inflammation and oxidative stress, suggesting that hepatic Cx43-based signaling may protect against acetaminophen-induced liver toxicity (Maes *et al.*, 2016a). In rat liver lobules treated with thioacetamide, disappearance of Cx32 at the cell borders of hepatocytes is observed. In primary cultures of rat hepatocytes, IL-1β causes the loss of Cx32. These effects are mitigated by a mitogen-activated protein kinase and p38 mitogen-activated protein inhibitor, respectively. This demonstrates the involvement of these signal transduction pathways in the regulation of Cx32 during the acute-phase response to IL-1β (Yamamoto *et al.*, 2004).

2.5 Stomach and intestine

At least 10 different Cx types are expressed in the intestinal tract. Cx26, Cx32, Cx36, Cx37, Cx40, Cx43, Cx45 and Cx57 are detected in the small intestine of several species, whereas Cx26, Cx31, Cx31.1, Cx32, Cx36, Cx40, Cx43 and Cx45 are present in the colon (Table 1) (Maes *et al.*, 2015a). The stomach produces 3 Cx species with Cx26 in epithelial cells and *lamina propria* of the fundus (Fiertak *et al.*, 1999, Radebold *et al.*, 2001, Liu *et al.*, 2010), Cx32 in the glandular regions, specifically in foveolar cells (Kyoi *et al.*, 1992, Uchida *et al.*, 1995, Radebold *et al.*, 2001) and Cx43 in circular muscle layers in gastric tissue (Seki and Komuro, 2002, Nishitani *et al.*, 2005). These Cx proteins have been linked with an array of gastrointestinal features including motility, gastric acid secretion and intestinal innate immune defense (Maes *et al.*, 2015a).

Helicobacter pylori colonizes the gastric mucosa and harms the stomach by several mechanisms, such as produced ammonia, proteases, vacuolating cytotoxin A, phospholipases and cytotoxin associated gene (Cag) A (Smoot, 1997). Indeed, CagA-positive *Helicobacter pylori* can cause gastritis, an inflammatory reaction of the stomach lining, and thereby abolish GJIC in cultured human gastric epithelial cells (Tao *et al.*, 2007, Xu *et al.*, 2011), while Cx43 expression is diminished in cultured human gastric carcinoma cells (Xu *et al.*, 2007). Likewise, in gastric lesions of *Helicobacter pylori*-infected patients, Cx32 and Cx43 levels are reduced, especially with the CagA-positive variant (Jia *et al.*, 2008, Xu *et al.*, 2008a, Xu *et al.*, 2008b). *Shigella flexneri*, a species of Gram-negative bacteria, causes inflammation by invading the colonic mucosa. This induces the opening of Cx26-based HCs through actin and phospholipase C, which allows extracellular release of ATP (Tran Van Nhieu *et al.*, 2003, Simpson *et al.*, 2013). ATP is also found to be an early alert response to infection with enteric pathogens that eventually promote inflammation of

the gut. In colonic epithelium in mouse models of intestinal inflammation, Cx43 expression is lost completely (Sedhom *et al.*, 2013). Similarly, Cx43 levels are decreased in enterocytes in a mouse model of necrotizing enterocolitis. In this case, the release of IFN-γ suppresses GJIC by inducing the dephosphorylation and internalization of Cx43 (Leaphart *et al.*, 2007).

2.6 Skin

Skin, the largest organ of the body that forms a highly complex and organized protective barrier against the external environment, is constituted of 3 major layers, namely the epidermis, the dermis and the hypodermis. As the blood supply of the skin is limited to the 2 latter layers, cell-to-cell communication is necessary to provide signals and nutrients to the outer skin layers. In skin, a plethora of Cx proteins is expressed, including Cx26, Cx30, Cx30.3, Cx31, Cx31.1, Cx32, Cx37, Cx40, Cx43 and Cx45. Keratinocytes mainly produce Cx26 and Cx43 (Richard, 2000), while human dermal fibroblasts contain Cx43 and Cx45 and low quantities of Cx40 (Table 1) (Levit and White, 2015). These Cx species influence the coordination of cell proliferation, migration and differentiation events, thus maintaining epidermal homeostasis (Martin and van Steensel, 2015).

Mutations that cause inflammatory skin disease show dysregulated HCs composed of Cx26, Cx30, Cx31, and Cx43, as evidenced by extracellular ATP leakage and excessive cytosolic influx of calcium (Levit and White, 2015). Cx26 mutations, producing leaky HCs and disturbing GJ formation, can cause a diversity of skin diseases of which keratitis-ichthyosis-deafness is accompanied by inflammation (Scott *et al.*, 2012, Martin and van Steensel, 2015). During wound healing in rat and human, a process that involves inflammation, Cx26 and Cx30 levels are upregulated (Coutinho *et al.*, 2003, Brandner *et al.*, 2004, Sutcliffe *et al.*, 2015). In addition, hyperproliferation occurs and wound healing is suppressed by persistent expression of Cx26 in mouse epidermis. Mechanistically, ectopic expression of Cx26 in keratinocytes results in increased ATP release, which delays epidermal barrier recovery and promotes an inflammatory response in resident immune cells (Djalilian *et al.*, 2006). In contrast, Cx43 production is lost at wound sites and surrounding areas of the epidermis in rat (Goliger and Paul, 1995), mouse (Coutinho *et al.*, 2003) and human (Neub *et al.*, 2007), but continues to be expressed in diabetic wounds (Wang *et al.*, 2007). Bacterial cell wall components differentially influence expression levels and opening of Cx26-based (Donnelly *et al.*, 2012) and Cx43-based HCs (Robertson *et al.*, 2010). In this respect, peptidoglycan isolated from *S. aureus* promotes open HCs states in a human keratinocyte cell line transfected with keratitis-ichthyosis-deafness-associated Cx26 constructs. Furthermore, peptidoglycan stimulates ATP release into the extracellular milieu and increases IL-6 levels in human cervical cancer HeLa cells and human keratinocyte HaCaT cells expressing keratitis-ichthyosis-deafness mutants (Donnelly *et al.*, 2012). Gap27 accelerates wound healing and elevates cell proliferation in *ex vivo* models of wound healing (Evans and Leybaert, 2007, Wright *et al.*, 2009, Pollok *et al.*, 2011). Additionally, targeting Cx43 with ACT1, a peptide mimetic of the carboxyl-terminus of Cx43, accelerates fibroblast migration and proliferation, and wound reepithelialization in adults with chronic venous leg ulcers (Ghatnekar *et al.*, 2015). Similar promising results were obtained with antisense oligonucleotides targeting Cx43, improve wound closure events (Martin, 2015). When αCT1, a peptide based on the carboxyl-terminus of Cx43 is applied in the skin, a decreased

inflammatory response, reduced area of scar progenitor tissue, and restoration of more normal dermal structure and mechanical strength is found (Ongstad *et al.*, 2013). Furthermore, it has been found that $Cx43^{+/-}$ mice show accelerated re-epithelialization and wound closure, increases proliferation and activation of dermal fibroblasts, and enhances the expression of extracellular matrix remodeling mediators (Cogliati *et al.*, 2015).

2.7 Kidney

In kidney, Cx26, Cx30.3, Cx31, Cx32, Cx37, Cx40, Cx43, Cx45 and Cx46 are expressed, of which Cx37, Cx40, Cx43 and Cx45 are present in renal vasculature (Hanner *et al.*, 2010, Abed *et al.*, 2014a). Cx43 is found in vascular endothelium, smooth muscle of larger vessels, glomerular epithelial cells, proximal tubular cells and glomerular endothelial cells (Table 1) (Hillis *et al.*, 1997b). GJs are involved in several physiological and pathological processes in kidney (Wagner and Kurtz, 2013). Indeed, maintaining normal renal hemodynamics requires regulation of renal vascular conductance, endothelium-derived vasodilatation and autoregulatory mechanisms, all which are controlled by Cx-based signaling (Wagner *et al.*, 2007, Wagner *et al.*, 2010).

There is growing evidence of an intimate relation between Cx expression and the occurrence of inflammation in the kidney (Scheckenbach *et al.*, 2011, Abed *et al.*, 2014a). Cx37 and Cx40 are hereby considered anti-inflammatory renal Cx members, while Cx43 acts in a pro-inflammatory way (Abed *et al.*, 2014a, Abed *et al.*, 2014b). Cx43 is strongly expressed by inflammatory cells, damaged tubular cells and interstitial cells and in the endothelium of peritubular and glomerular capillaries at the early stages of hypertensive nephropathy in mouse (Toubas *et al.*, 2011). This pattern of Cx43 expression is very similar to that of intercellular adhesion molecule 1 and, to a lesser extent, of vascular cell adhesion molecule 1, both produced by renal endothelium in inflammatory conditions. Cx43 is therefore thought to be primarily implicated in tubule-interstitial inflammation (Hillis *et al.*, 1997a). Treatment of normal rat kidney epithelial cells with LPS results both in downregulation (Gerl *et al.*, 2014) and upregulation (Fernandez-Cobo *et al.*, 1998) of Cx43 expression. In contrast, Cx37, which is abundantly produced in the renal cortex of healthy mice, is markedly decreased in experimental models of chronic kidney disease (Toubas *et al.*, 2011). In a $Cx43^{+/-}$ mouse model of chronic kidney disease, the renal cortex shows a decrease of cell adhesion markers leading to reduced monocyte infiltration and interstitial renal fibrosis. Interestingly, treatment with Cx43 antisense oligonucleotides improves renal function in mice suffering from chronic kidney disease. Furthermore, Cx43-specific blockage, by the Gap26 mimetic peptide, inhibits monocyte adhesion in activated endothelium and profibrotic pathways in tubular cells (Abed *et al.*, 2014b).

2.8 Lung

Normal alveolar epithelium *in vivo* shows expression of Cx26, Cx32, Cx43 and Cx46 (Table 1) (Koval, 2002). Nevertheless, different Cx species, like Cx30 and Cx31, can be found in airway cell lines and airway cells in primary culture in non-differentiated and differentiated circumstances (Wiszniewski *et al.*, 2007). The continuous exposure to inhaled hostile factors makes lungs vulnerable to infection and inflammation. Therefore, proper tissue repair is of

utmost importance for maintaining lung homeostasis and relies on Cx-based signaling (Losa and Chanson, 2015).

Impairment of physiological Cx expression in lung is associated with an abnormal immune response in cystic fibrosis, a genetic disease in which lungs become clogged due to mucus secretion (Chanson *et al.*, 2001, Huang *et al.*, 2003a, Huang *et al.*, 2003b). In bronchiolar epithelial cells, loss of Cx37 expression is linked to allergic airway disease and cytokine production by T-helper cells (Park *et al.*, 2007). Cx43 is thought to be of importance for calcium signaling in lung tissue in inflammatory conditions, such as during acute lung injury and acute respiratory distress syndrome (MacCallum and Evans, 2005). Work with endothelial $Cx43^{-/-}$ mice demonstrates that Cx43 mediates calcium wave propagation that acts to amplify the inflammatory process (Parthasarathi *et al.*, 2006). Calcium waves are known to underlie leukocyte rolling in the vascular surface and blocking of Cx43-based channels by peptides results in reduction of neutrophil adhesion to the endothelial cell surface in a mouse pneumocyte cell line (Parthasarathi *et al.*, 2006, Sarieddine *et al.*, 2009). This pro-inflammatory role of Cx43 has been confirmed in vascular endothelium-specific $Cx43^{-/-}$ mice, exhibiting a decrease in neutrophil recruitment after LPS-induced lung inflammation (Sarieddine *et al.*, 2009). In cultured human pulmonary endothelial cells treated with LPS, mRNA and protein levels of Cx43 as well as GJIC are increased. The decrease of transendothelial resistance triggered by LPS hereby is attenuated following small interfering RNA-mediated suppression of Cx43 production (O'Donnell *et al.*, 2014). Cx40 expression is diminished in lung of mouse and rabbit suffering from acute lung injury induced by intranasal instillation of LPS. However, no differences in pulmonary inflammation are noticed in $Cx40^{+/-}$ mice in comparison with wild-type animals (Rignault *et al.*, 2007). In a endothelial cell-specific $Cx40^{-/-}$ mouse model, downregulated production of cluster of differentiation 73 is observed (Chadjichristos *et al.*, 2010). The latter seems to play a protective role in acute lung injury by preventing leukocyte adhesion to the endothelium (Thompson *et al.*, 2004, Volmer *et al.*, 2006).

2.9 Eye

Cx family members identified in the eye include Cx26, Cx30, Cx30.2, Cx32, Cx36, Cx37, Cx43, Cx45, Cx46, Cx50 and Cx57 (Table 1). Cx43 is expressed in multiple cell types of the eyes, including astrocytes, Müller cells, microglia, retinal pigment epithelium and endothelial cells and supports many aspects of eye development and normal physiology, but is equally involved in corneal inflammation (Danesh-Meyer *et al.*, 2015).

Cultured human corneal fibroblasts exposed to TNF-α show reduced Cx43 expression. These effects are attenuated by an inhibitor of c-jun terminal kinase, suggesting the involvement of both the mitogen-activated protein kinase signaling pathway and Cx43 production in corneal inflammation (Kimura *et al.*, 2013). Incubation of retinal pigment epithelial cells with glucose induces accumulation of IL-6, IL-8 and TGF-β, and negatively affects Cx43 levels and GJIC (Losso *et al.*, 2010).

Intense light exposure in albino rats increases Cx36 levels in the inner plexiform layer and lowers Cx45 quantities in the light-damaged retina, while Cx43 production becomes intensified in the retinal pigment epithelium and the choroid. In the latter, Cx43 colocalizes

with indicators of nitration-related oxidative stress, like nitrotyrosine, inflammatory markers, such as cluster of differentiation 45, and ionized calcium-binding adaptor molecule-1 (Guo *et al.*, 2014). A number of studies show that reducing Cx43 expression, or blocking channel function, in the eye can be beneficial. Treatment of corneal scrape wounds or laser ablations, mimicking photorefractive keratectomy, with Cx43 antisense oligonucleotides increases the rate of epithelial recovery, whilst significantly reducing oedema, myofibroblast differentiation and proliferation (Grupcheva *et al.*, 2012). This outcome has been confirmed using α-carboxy terminus 1, a Cx43 mimetic peptide, that also reduces healing time and inflammation in a rat model of corneal inflammation (Moore *et al.*, 2013). The Cx43 antisense oligonucleotides applied to humans with non-healing burns to the cornea under compassionate use promoted healing primarily by reducing inflammation and triggering vascular recovery to the limbus (Ormonde *et al.*, 2012). Interestingly, injection of Cx43 antisense oligonucleotides in a rabbit model of glaucoma results in less myofibroblast production and reduced scarring (Deva *et al.*, 2012). When used in patients with repeated trabeculectomy block owing to scarring, the Cx43 antisense oligonucleotides reduces scarring and resulted in long term maintenance of normal intraocular pressure (Becker *et al.*, 2016). In a rat retina ischemia/reperfusion model, delivery of Peptide5, either systemically (Danesh-Meyer *et al.*, 2012) or by intravitreal injection, considerably reduces vessel leak, significantly counteracts inflammation and promotes neuronal survival (Chen *et al.*, 2013, Chen *et al.*, 2015). Although Cx43 levels may be reduced in the diabetic retinal vessel bed (Tien *et al.*, 2014, Tien *et al.*, 2015), animal models and direct analysis of human donor tissues reveals very high levels of Cx43 associated with vessel endothelium, astrocytes and Müller cells near diabetic retinopathy lesions.

2.10 Immune cells

The immune system provides a variety of defenses against PAMPs and DAMPs. This occurs through the establishment of physical and chemical barriers and the concerted actions of a wide spectrum of biochemical mediators and immune cells (Glass *et al.*, 2015). The expression and functional significance of several Cx family members, including Cx30.3, Cx32, Cx37, Cx40 and Cx43 (Table 1), have been documented in cells and tissues of the immune and lymphatic system (Oviedo-Orta and Howard Evans, 2004, Neijssen *et al.*, 2007). Cx43 is by far the most important Cx species in the immune system, being found in macrophages, neutrophils, dendritic cells, B-cells and T-cells (Glass *et al.*, 2015). Cx43 fulfills different functions, such as recruitment of neutrophils and T-cell activation (Glass *et al.*, 2015). Circulating monocytes contain Cx43 and its expression is increased upon LPS treatment. The latter, together with IFN-γ, seems a prerequisite for establishing GJIC between cultured monocytes (Eugenín *et al.*, 2003). This suggests that Cx43 may be of importance in the formation of GJIC in macrophages (Alves *et al.*, 1996). Human tonsillar B-lymphocytes also express Cx43, which is upregulated *in vitro* after exposure to LPS (Oviedo-Orta *et al.*, 2000).

In the presence of GJ and HC inhibitors, such as 18β-glycyrrhetinic acid or Cx mimetic peptides, cultured human lymphocytes produce less immunoglobulins M, G and A in response to phytohaemagglutinin activation. This indicates that inhibition of Cx43-based channels may result in disrupted communication between T-cells and B-cells or in

abrogation of immunoglobulin production (Oviedo-Orta *et al.*, 2001). Moreover, dye coupling is present between dendritic cells, suggesting that Cx43 is capable of forming functional GJs between these cells. Decreased dendritic cells activation and antigen presentation are observed when cells are treated with Gap27 following exposure to IFN-γ and LPS (Matsue *et al.*, 2006). Using different Cx blocking agents, it has been found that polymorphonuclear leukocytes release ATP through Cx43-based HCs in a protein/phosphatase-A-dependent manner. This is confirmed in polymorphonuclear leukocytes derived from $Cx43^{fl/fl}$ mice, whereby activated polymorphonuclear leukocytes display decreased extracellular ATP liberation (Eltzschig *et al.*, 2006). The release of ATP possibly plays a role in perpetuation of the inflammasome cycle in chronic disease conditions (Kim *et al.*, 2016).

2.11 Other organs

Electrical and metabolic coupling between pancreatic β-cells is required for proper insulin secretion and effective glycemic control. In particular, β-cell-specific GJIC relies on Cx36-based GJs, which ensure orchestrated insulin release across islets (Cigliola *et al.*, 2013). Other Cx proteins identified in pancreas are Cx43, Cx45 and Cx32 (Charollais *et al.*, 1999) (Table 1). $Cx32^{-/-}$ mice exhibit a deleterious course of acute pancreatitis with increased necrosis, oedema and inflammation of the exocrine pancreas (Frossard *et al.*, 2003). In cerulein-induced pancreatitis, irsogladine, an enhancer of GJIC, lowers the severity of the disease, decreases serum and pancreatic amylase. This coincides with disappearance of Cx32 in the pancreatic acini (Ito *et al.*, 1997). This is not the case in a similar model in rat, where Cx32 mRNA and protein levels are both increased upon induction of pancreatitis with cerulein (Ogoshi *et al.*, 2002).

Myoblasts express several Cx proteins, of which Cx39, Cx40, Cx43 and Cx45 are present in developing myoblasts and injured adult skeletal muscle (Table 1) (Merrifield and Laird, 2015). Cx43 has been detected in prefusional C2C12 myoblasts (Constantin and Cronier, 2000) and in primary cultures, and drives the differentiation and regeneration of the skeletal muscle (Araya *et al.*, 2005). Transient expression of Cx40 has been described in axial skeletal muscles of mouse embryos during myoblast fusion (Dahl *et al.*, 1995). Other Cx species found in muscle include Cx39 and Cx45 (von Maltzahn *et al.*, 2004, von Maltzahn *et al.*, 2011). Denervation of fast skeletal muscle cells activates NF-κB and elevates mRNA levels of TNF-α and IL-1β, which clearly shows the onset of inflammation after denervation. These effects cannot be reproduced in $Cx43^{fl/fl}Cx45^{fl/fl}$ mice. Interestingly, denervated myofibers display *de novo* formation of HCs composed of Cx39, Cx43, and Cx45 as well as increased expression of purinergic P2X7 receptors (Cea *et al.*, 2013). Furthermore, when exposing cultured microvascular endothelial cells from murine skeletal muscle to LPS and hypoxia/reoxygenation, protein kinase A-specific phosphorylation of Cx40 is more reduced when compared to exposure to LPS or hypoxia/reoxygenation alone. This occurs through diminished electrical coupling between microvascular endothelial cells, which indicates phosphorylation-driven involvement of Cx40 in inflammation and ischemia/reperfusion (Bolon *et al.*, 2008).

Cx43 is the most abundantly expressed Cx species in bone, including osteocytes, osteoblasts and osteoclasts (Civitelli *et al.*, 1993, Donahue *et al.*, 1995). In addition, Cx45 and Cx46 are present in osteoblastic cells (Chaible *et al.*, 2011, Plotkin and Bellido, 2013) and Cx37 production is found in osteoblasts, osteocytes and osteoclasts (Paic *et al.*, 2009, Pacheco-Costa *et al.*, 2014), while chondrocytes are positive for Cx43, Cx45, Cx32 and Cx46 (Mayan *et al.*, 2013). Expression of Cx43 (Su *et al.*, 1997, Kato *et al.*, 2013), Cx32 (Yamaoka *et al.*, 2000b), Cx40 and Cx45 (Yamaoka *et al.*, 2002) has been demonstrated in cells of periodontal ligaments (Table 1). In cartilage in osteoarthritic shoulders, Cx43, collagen type I, and TNF-α levels are increased (Casagrande *et al.*, 2015). This also holds true for fibroblast-like synoviocytes exposed to LPS. Treatment of collagen-induced arthritic rats with small interfering RNA directed against Cx43 ameliorates paw swelling and reduces the manifestation of arthritis (Tsuchida *et al.*, 2013). These findings indicate that suppression of Cx43 production has an anti-inflammatory outcome in rat and efficiently counteracts arthritis. Increasing Cx43 expression enhances the production of IL-1 and IL-6, and increases the secretion of collagenases into conditioned cell culture medium of cultured synovial fibroblasts. Conversely, knockdown of Cx43 production by small interfering RNA decreases expression of many of these inflammatory genes (Gupta *et al.*, 2014).

3 Conclusions

Inflammatory diseases, such as multiple sclerosis, atherosclerosis, arthritis, gastritis and non-alcoholic steatohepatitis, affect millions of people worldwide. In the last decade, Cx proteins and their channels have been extensively studied in inflammatory conditions in a broad spectrum of tissues and cells. Collectively, these efforts show that Cx proteins play an important role in inflammatory processes in various organs, including brain, heart, blood vessels, liver, intestines, skin, lung and eye (Kwak *et al.*, 2002, Sarieddine *et al.*, 2009, Scheckenbach *et al.*, 2011, Martin *et al.*, 2014, Glass *et al.*, 2015, Maes *et al.*, 2015b, Meens *et al.*, 2015). A number of experimental tools, such as genetically altered animals (Parthasarathi *et al.*, 2006, Wong *et al.*, 2006, Markoullis *et al.*, 2012a, Abed *et al.*, 2014b, Sagawa *et al.*, 2015), small interfering RNA duplexes (Tsuchida *et al.*, 2013, Gupta *et al.*, 2014), HC blockers and GJ inhibitors (Matsue *et al.*, 2006, Chanson and Kwak, 2007, O'Carroll *et al.*, 2008, Deva *et al.*, 2012, Wang *et al.*, 2013c, Abed *et al.*, 2014b), have allowed to gain a better insight into the molecular mechanisms underlying the involvement of Cx signaling in inflammation. Although to be considered with a lot of caution, genetic knockout experiments suggest that Cx43 seems to be a mainly pro-inflammatory Cx (Parthasarathi *et al.*, 2006, Huang *et al.*, 2012, Abed *et al.*, 2014b), while Cx32 and Cx37 are rather anti-inflammatory (Table 3) (Frossard *et al.*, 2003, Parthasarathi *et al.*, 2006, Wong *et al.*, 2006, Abed *et al.*, 2014b, Sagawa *et al.*, 2015). This is substantiated by studies that apply a variety of Cx-based channel blockers (Wright *et al.*, 2009, Froger *et al.*, 2010, Pollok *et al.*, 2011, Deva *et al.*, 2012, Wang *et al.*, 2013c, Chever *et al.*, 2014). Nevertheless, most of the presently used Cx-based channel blockers inhibit GJs and HCs (Bodendiek and Raman, 2010). Two potential exceptions include Gap19, which suppresses Cx43-based HC activity without affecting GJIC (Iyyathurai *et al.*, 2013, Abudara *et al.*, 2014), and Peptide5 (O'Carroll *et al.*, 2008). Peptide5 has been successfully delivered directly and systemically in a number of animal models, and owing to its extracellular acting mode of action, can be

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targeted to disease and injury sites. Gap19 needs to cross the plasma membrane to be effective and is more difficult to target, but its asset is the very selective HC blocking capability without reducing GJIC. Since Cx43-based HCs are often associated with pathological conditions, Gap19 and Peptide5, or similar extracellular acting peptides (Evans, 2015), could be of great value in the further investigation of the role of HCs in inflammation (Wang *et al.*, 2013c, Abed *et al.*, 2014b).

Overall, it can be concluded that Cxs and their channels play an important role in the inflammatory process and hence in a great number of highly prevalent diseases. This may provide opportunities for the search of novel drug targets and therapeutics for the clinical treatment of inflammatory diseases.

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Abbreviations

ATP	adenosine triphosphate
Cag	cytotoxin associated gene
CL	cytoplasmic loop
Cx	connexin
DAMPs	damage-associated molecular patterns
EL	extracellular loop
FGF	fibroblast growth factor
GJ(s)	gap junction(s)
GJIC	gap junctional intercellular communication
HC(s)	hemichannel(s)
IFN	interferon
IL	interleukin
LPS	lipopolysaccharide
NF	nuclear factor
NO(S)	nitric oxide (synthase)
PAMPs	pathogen-associated molecular patterns

TGF	transforming growth factor
TM	transmembrane domain
TNF	tumor necrosis factor

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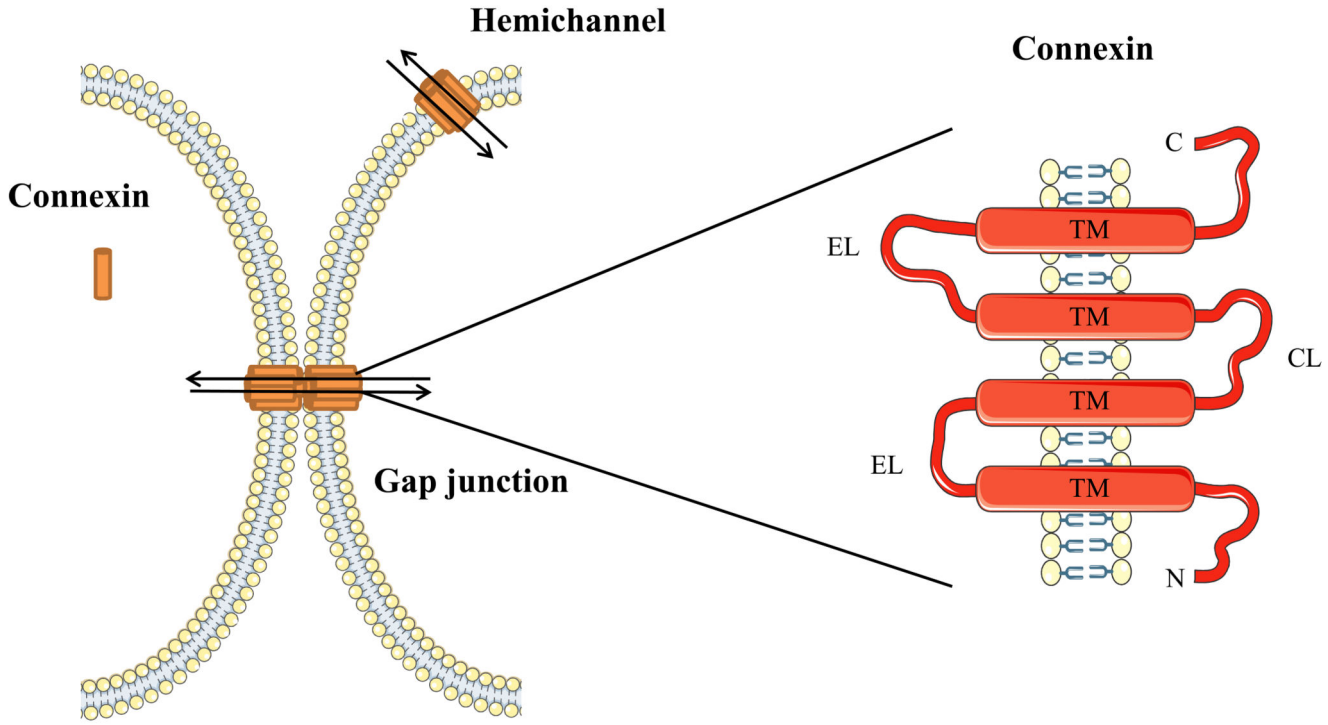

Figure 1. Structure of connexins and their channels.

GJs appear as plaques at the cell plasma membrane surface and are formed by the interaction of 2 HCs of adjacent cells. Each HC is composed of 6 Cx proteins, which are transmembrane proteins consisting of a cytoplasmic loop, 2 extracellular loops, a cytoplasmic *C*-terminal tail and a cytoplasmic *N*-terminal tail. (CL, cytoplasmic loop; EL, extracellular loop; TM, transmembrane domain).

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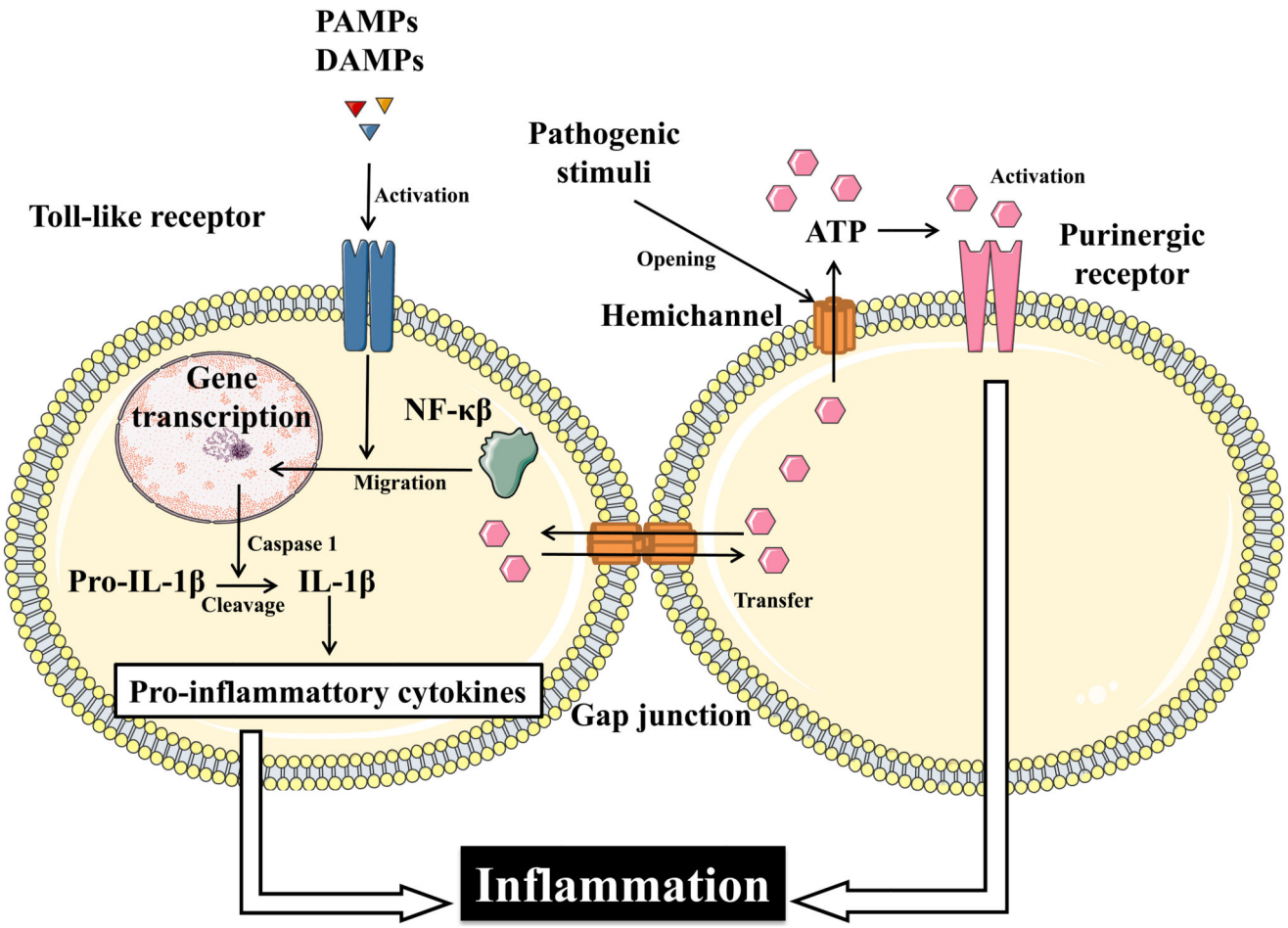

Figure 2. Role of connexin signaling in the initiation of inflammation.

PAMPs or DAMPs can interact with Toll-like receptors, which undergo dimerization upon activation. This triggers the migration of NF-κβ to the nucleus, where it activates gene transcription of pro-IL-1β. The latter is cleaved to mature IL-1β by caspase 1 in the cytosol, which influences the production of a number of pro-inflammatory mediators, such as TNF-α, IL-6 and NOS. This characterizes the onset of the inflammatory reaction. GJs can transfer ATP between neighboring cells. HCs can release ATP into the extracellular environment after opening by pathogenic stimuli. ATP can then interact with P2X7 purinergic receptors at the cell plasma membrane and can influence the inflammatory process. (ATP, adenosine triphosphate; DAMPs, damage-associated molecular patterns; IL, interleukin; NF, nuclear factor; NOS, nitric oxide synthase; PAMPS, pathogen-associated molecular patterns; TNF, tumor necrosis factor).

Table 1

Connexin expression in different organs.

(Cx, connexin).

Organ	Cell type	Cx species	Reference
Brain	Astrocytes	Cx30, Cx43	(Dermietzel *et al.*, 1991, Nagy and Rash, 2000)
	Microglial cells	Cx26, Cx32	(Eugenín *et al.*, 2001, Parenti *et al.*, 2002, Garg *et al.*, 2005, Takeuchi *et al.*, 2006, Kielian, 2008)
	Oligodendrocytes	Cx32, Cx47, Cx29	(Dermietzel *et al.*, 1989, Altevogt *et al.*, 2002, Odermatt *et al.*, 2003)
	Neurons	Cx36, Cx45	(Takeuchi and Suzumura, 2014)
	Blood-brain barrier endothelial cells	Cx37, Cx40, Cx43	(Little *et al.*, 1995, Traub *et al.*, 1998, Nagasawa *et al.*, 2006, De Bock *et al.*, 2014)
	Blood-brain barrier pericytes	Cx37, Cx40, Cx43	(Little *et al.*, 1995, Traub *et al.*, 1998, Nagasawa *et al.*, 2006, De Bock *et al.*, 2014)
Heart	Smooth muscle cells	Cx40, Cx43, Cx45	(Gros and Jongsma, 1996, Severs *et al.*, 2004)
	Cardiomyocytes	Cx40, Cx43, Cx45	(Gros and Jongsma, 1996, Severs *et al.*, 2004)
Blood vessels	Endothelial cells	Cx43, Cx37, Cx40	(Chadjichristos *et al.*, 2010, Scheckenbach *et al.*, 2011)
	Smooth muscle cells	Cx43, Cx45, Cx40, Cx37	(Chadjichristos *et al.*, 2010, Scheckenbach *et al.*, 2011)
Liver	Sinusoidal endothelial cells	Cx26, Cx43	(Hernández-Guerra *et al.*, 2014)
	Hepatic arteries and portal vein endothelial cells	Cx37, Cx40	(Fischer *et al.*, 2005, Shiojiri *et al.*, 2006)
	Hepatocytes	Cx26, Cx32	(Kyoi *et al.*, 1992, Ohkusa *et al.*, 1995, Iwata *et al.*, 1998, Radebold *et al.*, 2001)
	Kupffer cells	Cx26, Cx43	(González *et al.*, 2002, Eugenín *et al.*, 2007)
	Stellate cells	Cx26, Cx43	(Fischer *et al.*, 2005, Maes *et al.*, 2015b)
Stomach and intestines	Stomach	Cx26, Cx32, Cx40, Cx43, Cx45	(Wang and Daniel, 2001, Cousins *et al.*, 2003, Liu *et al.*, 2010, Wang *et al.*, 2014)
	Foveolar cell	Cx32	(Fink *et al.*, 2006)
	Small intestine	Cx26, Cx31, Cx57	(Filippov *et al.*, 2003)
	Musculus externa cell	Cx40, Cx43	(Wang and Daniel, 2001, Liu *et al.*, 2008)
	Myenteric plexus cell	Cx36, Cx40, Cx43, Cx45	(Wang and Daniel, 2001, Liu *et al.*, 2008, Frinchi *et al.*, 2013)
	Epithelial cell	Cx32, Cx37, Cx43	(Traoré *et al.*, 2003, Husøy *et al.*, 2004, Hakim *et al.*, 2008)
	Interstitial cell of cajal	Cx43	(Seki and Komuro, 2002)
	Colon	Cx31, Cx31.9, Cx43	(Ismail *et al.*, 2014, Li *et al.*, 2015b)
	Musculus externa cell	Cx26, Cx40, Cx43	(Wang and Daniel, 2001, Mattii *et al.*, 2013)
	Myenteric plexus cell	Cx36, Cx40, Cx43, Cx45	(Wang and Daniel, 2001, Frinchi *et al.*, 2013, McClain *et al.*, 2014)
	Epithelial cell	Cx26, Cx32, Cx37, Cx43	(Kanczuga-Koda *et al.*, 2004, Kanady *et al.*, 2015)
	Muscularis mucosa cell	Cx43	(Ismail *et al.*, 2014)
	Interstitial cell of Cajal	Cx43	(Nemeth *et al.*, 2000)

Organ	Cell type	Cx species	Reference
Skin	Keratinocytes	Cx26, Cx30.3, Cx30, Cx31.1, Cx31, Cx40, Cx43, Cx45	(Di *et al.*, 2001, Brandner *et al.*, 2004, Wang *et al.*, 2007, Churko and Laird, 2013, Martin *et al.*, 2014)
	Fibroblasts	Cx43, Cx45, Cx40	(Wright *et al.*, 2009, Meyer *et al.*, 2014, Cogliati *et al.*, 2015, Tarzemany *et al.*, 2015)
	Melanocytes	Cx43	(Haass *et al.*, 2004, Rezze *et al.*, 2011, Penuela *et al.*, 2012)
Kidney	Smooth muscle cells	Cx37, Cx45	(Arensbak *et al.*, 2001, Hanner *et al.*, 2010, Li *et al.*, 2015a)
	Podocytes	Cx43, Cx45	(Hanner *et al.*, 2010, Morioka *et al.*, 2013, Yang *et al.*, 2014)
	Pericytes	Cx37	(Zhang *et al.*, 2006, Hanner *et al.*, 2010)
	Mesangial cells	Cx40, Cx45	(Arensbak *et al.*, 2001, Kurtz *et al.*, 2007, Hanner *et al.*, 2010, Morioka *et al.*, 2013)
Lung	Alveolar epithelium	Cx26, Cx32, Cx43, Cx46	(Koval, 2002)
Eye	Lens epithelial cells	Cx43, Cx50	(Berthoud *et al.*, 2014)
Immune cells	T-cells	Cx40, Cx43	(Oviedo-Orta *et al.*, 2000)
	B-cells	Cx40, Cx43	(Oviedo-Orta *et al.*, 2000)
	Monocytes	Cx43	(Navab *et al.*, 1991)
	Macrophages	Cx37, Cx43	(Beyer and Steinberg, 1991, Alves *et al.*, 1996, Kwak *et al.*, 2002)
Pancreas	β-cells	Cx36, Cx43, Cx45	(Charollais *et al.*, 1999)
	Exocrine pancreas	Cx32	(Frossard *et al.*, 2003)
Skeletal muscle	Myoblasts	Cx39, Cx40, Cx43, Cx45	(Merrifield and Laird, 2015)
Bone	Osteocytes	Cx37, Cx43	(Krüger *et al.*, 2000, Paic *et al.*, 2009, Pacheco-Costa *et al.*, 2014)
	Osteoblasts	Cx37, Cx43, Cx45, Cx46	(Civitelli *et al.*, 1993, Donahue *et al.*, 1995, Krüger *et al.*, 2000, Chaible *et al.*, 2011, Plotkin and Bellido, 2013)
	Osteoclasts	Cx37, Cx43	(Paic *et al.*, 2009, Pacheco-Costa *et al.*, 2014)
	Chondrocytes	Cx32, Cx43, Cx45, Cx46	(Mayan *et al.*, 2013)

Table 2

Effects of inflammation on connexins and their channels.

(Cx, connexin; FGF, fibroblast growth factor; GJIC, gap junctional intercellular communication; HC, hemichannel; IFN, interferon; IL, interleukin; LPS, lipopolysaccharide; mRNA, messenger ribonucleic acid; TGF, transforming growth factor; TNF, tumor necrosis factor).

Tissue	Model	Outcome	Reference
Brain	Multiple sclerosis autoimmune encephalitis in mice	↓ Cx32-based and Cx47-based GJs in oligodendrocytes ↓ Cx43-based GJs in astrocytes	(Markoullis *et al.*, 2012a)
	Multiple sclerosis patients	↓ Cx32-based and Cx47-based GJs in oligodendrocytes ↑ Cx30 and Cx43 protein in cortical lesions	(Lieury *et al.*, 2014, Markoullis *et al.*, 2014)
	Rasmussen encephalitis patients	↓ Cx32 protein in cortex = Cx26 protein in cortex	(Cepeda *et al.*, 2015)
	Intracerebroventricular injection of LPS in rats	↑ Cx32 mRNA in hippocampus ↑ Cx30 and Cx32 mRNA in hippocampus ↓ Cx43 protein in hippocampus	(Abbasian *et al.*, 2013) (Abbasian *et al.*, 2012) (Sayyah *et al.*, 2012)
	IL-1β-treated primary human fetal astrocytes	↓ GJIC ↓ Cx43 mRNA and protein	(John *et al.*, 1999, Duffy *et al.*, 2000)
	TNF-α-treated primary rat astrocytes	↓ GJIC Cx43 phosphorylation	(Haghikia *et al.*, 2008b)
	IL-1β and TNF-α-treated primary mouse astrocytes	↓ Cx43 protein and GJIC	(Même *et al.*, 2006)
	LPS-treated primary rat astrocytes	↓ GJIC	(Bolaños and Medina, 1996)
	TNF-α and IFN-γ-treated spinal rat astrocytes	↓ Cx43 mRNA, protein and GJIC	(Zhang *et al.*, 2013b, Zhang *et al.*, 2015)
	LPS-treated co-culture of rat primary astrocytes and rat primary microglia	↓ GJIC	(Haghikia *et al.*, 2008a, Hinkerohe *et al.*, 2010)
	LPS-treated co-culture of mouse primary astrocytes and mouse primary microglia	↓ GJIC ↑ HC activity	(De Vuyst *et al.*, 2007, Fruscione *et al.*, 2011) (Retamal *et al.*, 2007, Froger *et al.*, 2009)
	LPS-treated primary neonatal astrocytes	↓ Cx43 mRNA, protein and GJIC	(Liao *et al.*, 2010)
	LPS-treated mouse microglia	↓ Cx32 mRNA, protein and GJIC	(Takeuchi *et al.*, 2006)
	S. aureus-treated mouse brain slices	↑ HC activity ↓ GJIC ↑ Cx43 and Cx30 protein	(Karpuk *et al.*, 2011)
	Peptidoglycan-treated mouse primary microglia	↓ GJIC ↓ Cx43 and Cx30 mRNA and protein ↑ Cx26 mRNA and protein	(Garg *et al.*, 2005)
	Protozoan-treated rat astrocytes and leptomeningeal cells	↓ GJIC	(Campos de Carvalho *et al.*, 1998, Mele and Madrenas, 2010)
	Human immunodeficiency virus-infected human astrocytes	↑ Cx43-based HC activity ↓ GJIC	(Orellana *et al.*, 2014)
	Mouse hepatitis virus-infected astrocytes and mice	↓ Cx43 protein ↓ GJIC	(Basu *et al.*, 2015)
	Peptidoglycan-treated immortalized mouse endothelial cells	↑ Cx43-based HC activity	(Robertson *et al.*, 2010)

Tissue	Model	Outcome	Reference
	Spinal cord injury in rats	↑ Cx43 protein and mRNA in astrocytes = Cx32 and Cx36 protein and mRNA	(Lee *et al.*, 2005)
	FGF-1-treated spinal astrocytes	↑ Cx43-based HC activity	(Garré *et al.*, 2010)
Heart	Injection of LPS in rats	↓ Cx43 mRNA	(Fernandez-Cobo *et al.*, 1999)
	TNF-α-treated rat myoblast cell line	↓ Cx43 promotor activity	(Fernandez-Cobo *et al.*, 1999)
	TGF-β-treated mouse embryotic cardiomyocytes	↓ GJIC	(Waghabi *et al.*, 2009)
	T. cruzi-infected mouse embryotic cardiomyocytes	↓ GJIC	(Waghabi *et al.*, 2009)
	T. cruzi-infected patients	↓ Cx43 protein	(Waghabi *et al.*, 2009)
	T. cruzi-infected mouse cardiomyocytes	↑ Cx43 protein on short term ↓ Cx43 protein on long term	(Adesse *et al.*, 2008)
Blood vessels	Hyperlipidemic mice	↓ Cx40 protein in endothelium ↓ Cx37 protein in endothelium ↑ Cx43 protein in endothelium	(Yeh *et al.*, 2003)
	Atherosclerotic mice	↓ Cx40 protein in endothelium ↓ Cx37 protein in endothelium	(Kwak *et al.*, 2002)
	Endothelium exposed to oxidative stress, prothrombotic molecules and cytokines	↓ Cx40 protein ↓ Cx37 protein	(Hou *et al.*, 2008)
	Coronary atherosclerosis patients	↑ Cx43 protein in coronary artery	(Blackburn *et al.*, 1995)
	LPS-injected rats	↑ Cx40 protein in aorta	(Frimmel *et al.*, 2014)
	TNF-α-treated human umbilical vein endothelial cells	↓ Cx37 mRNA ↓ Cx40 mRNA	(van Rijen *et al.*, 1998)
	LPS-injected mice	↓ Cx37 protein in aortic endothelium ↓ Cx40 protein in aortic endothelium	(Simon *et al.*, 2004)
Liver	LPS-treated mice	↓ Cx32 and Cx26 protein ↓ Cx32 mRNA ↓ GJIC	(De Maio *et al.*, 2000, Correa *et al.*, 2004)
	Hepatitis patients	↓ Cx32 protein	(Yamaoka *et al.*, 2000a, Nakashima *et al.*, 2004)
	IL-1β-treated primary hepatocytes	↓ Cx32 protein	(Yamamoto *et al.*, 2004)
	IL-1, IL-6 and TNF-α-treated immortalized hepatocytes	↑ Cx26 mRNA	(Temme *et al.*, 1998)
	LPS-treated mice	↑ Cx26 mRNA	(Temme *et al.*, 2000)
	LPS and IL-1β-treated primary stellate cell cultures	↑ Cx43 mRNA	(Fischer *et al.*, 2005)
	LPS-treated primary Kupffer cell cultures	↑ Cx43 mRNA	(González *et al.*, 2002, Eugenín *et al.*, 2007)
	LPS and IFN-γ-treated primary Kupffer cell cultures	↑ Cx43 protein and mRNA	(Eugenín *et al.*, 2007)
	Acetaminophen-treated mice	↑ Cx43 protein and mRNA in liver ↑ Cx43 protein in hepatocytes ↓ Cx32 and Cx26 protein and mRNA in liver	(Maes *et al.*, 2016a)
Stomach and intestines	Atrophic gastritis in rats	↓ Cx32 protein	(Nagahara *et al.*, 1996, Miwa *et al.*, 1997)

Tissue	Model	Outcome	Reference
	Intestinal inflammation in mouse	↓ Cx43 protein in colonic epithelium	(Sedhom *et al.*, 2013)
	Necrotizing enterocolitits in mouse	↓ Cx43 protein in enterocytes ↓ GJIC	(Leaphart *et al.*, 2007)
	S. flexneri-infected human Cx26-transfected HeLa cells	↑ HC activity	(Tran Van Nhieu *et al.*, 2003, Man *et al.*, 2007)
	S. flexneri-infected human mutated Cx26-transfected HeLa cells	= HC activity	(Man *et al.*, 2007)
	S. flexneri-infected human Cx30-transfected HeLa cells	= HC activity	(Man *et al.*, 2007)
	S. flexneri-infected human Cx31-transfected HeLa cells	= HC activity	(Man *et al.*, 2007)
	S. flexneri-infected human Caco-2/TC7 intestinal epithelial cells	↑ HC activity	(Clair *et al.*, 2008)
	Yersinia enterocolitica-infected Cx43-transfected human cells	↑ HC activity ↑ Cx43 phosphorylation	(Wong and Isberg, 2005)
	Helicobacter pylory-infected human gastric epithelial cells	↓ GJIC	(Yokoyama *et al.*, 2005)
Skin	Wound healing in rat	↑ Cx26 protein in epidermis ↑ Cx30 protein in epidermis	(Coutinho *et al.*, 2003, Sutcliffe *et al.*, 2015)
	Wound healing in human	↑ Cx26 protein in skin slices ↑ Cx30 protein in skin slices	(Brandner *et al.*, 2004, Sutcliffe *et al.*, 2015)
	Wounded epidermis of rat	↓ Cx43 protein	(Goliger and Paul, 1995)
	Wounded epidermis of mice	↓ Cx43 protein	(Coutinho *et al.*, 2003)
	Wounded epidermis of human	↓ Cx43 protein	(Neub *et al.*, 2007)
	Diabetic wound in rat	↓ Cx43 protein in epidermis ↓ Cx26 protein in epidermis ↑ Cx43 protein in dermis	(Wang *et al.*, 2007)
	Peptidoglycan (*S. epidermidis*)-treated mouse endothelial cells	↑ GJIC ↑ HC activity ↑ Cx43 protein	(Robertson *et al.*, 2010)
	Peptidoglycan (*S. epidermidis* and *S. aureus*)-treated keratinocytes	↑ Cx26-based HCs	(Donnelly *et al.*, 2012)
	Peptidoglycan (*S. epidermidis* and *S. aureus*)-treated HeLa cells	↑ Cx26-based HCs	(Donnelly *et al.*, 2012)
Kidney	LPS-treated rat kidney epithelial cells	↓ Cx43	(Gerl *et al.*, 2014)
	LPS-treated rat kidney epithelial cells	↑ Cx43	(Fernandez-Cobo *et al.*, 1998)
	Glucose-treated human cortical collecting duct cells	↑ Cx43 protein and mRNA through TGF-β1	(Hills *et al.*, 2009)
	Chronic kidney-diseased mice	↓ Cx37 protein and mRNA	(Toubas *et al.*, 2011)
	Chronic kidney-diseased patients	↑ Cx43 protein	(Abed *et al.*, 2014b)
	TGF-β1 human collecting duct cells	↑ Cx43 protein ↑ GJIC	(Hills *et al.*, 2009)
	Tubulointerstitial inflammation in humans	↑ Cx43 protein	(Hillis *et al.*, 1997a)
Lung	Ovalbumin-induced allergic airway disease in mice	↓ Cx37 protein and mRNA	(Park *et al.*, 2007)
	LPS-treated human pulmonary endothelial cells	↑ Cx43 protein ↑ GJIC	(O'Donnell *et al.*, 2014, Kandasamy *et al.*, 2015)

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Tissue	Model	Outcome	Reference
	Acute lung injury in rabbit	↓ Cx40 protein	(Rignault *et al.*, 2007)
Eye	TNF-α-exposed human corneal fibroblasts	↓ Cx43 protein	(Kimura *et al.*, 2013)
	Glucose-treated retinal pigment epithelial cells	↓ Cx43 protein ↓ GJIC	(Losso *et al.*, 2010)
	Intense light exposure in albino rats	↑ Cx36 protein in inner plexiform layer ↓ Cx45 protein in retina ↑ Cx43 protein in choroid	(Guo *et al.*, 2014)
	Diabetic retinal vessel	↓ Cx43 protein	(Tien *et al.*, 2014, Tien *et al.*, 2015)
Immune cells	LPS-treated monocytes	↑ Cx43 protein and mRNA	(Eugenín *et al.*, 2003)
	LPS-treated human tonsillar B-lymphocytes	↑ Cx43 protein and mRNA	(Oviedo-Orta *et al.*, 2000)
Skeletal muscle	Denervated myofibers	*De novo* expression Cx39-based, Cx43-based and Cx45-based HCs	(Cea *et al.*, 2013)
Bone	Osteoarthritic shoulders	↑ Cx43 protein in cartilage	(Casagrande *et al.*, 2015)
	LPS-treated fibroblast-like synoviocytes	↑ Cx43 mRNA	(Tsuchida *et al.*, 2013)

Table 3

Roles of connexins and their channels in inflammation.

(ATP, adenosine triphosphate; Cx, connexin; HC, hemichannel; IFN, interferon; IL, interleukin; LPS, lipopolysaccharide; TNF, tumor necrosis factor).

Tissue	Model	Outcome	Reference
Brain	Cx43 blocking in cytokine-treated astrocytes	↓ neurotoxicity	(Froger *et al.*, 2010)
	Multiple sclerosis autoimmune encephalitits in $Cx32^{-/-}$ mice	↓ loss of Cx47 and Cx43-based GJs	(Markoullis *et al.*, 2012a)
	Autoimmune encephalitic in astrocyte-specific $Cx43^{fl/fl}Cx30^{-/-}$ mice	No alteration in susceptibility or severity of encephalitis	(Lutz *et al.*, 2012)
	Cx43 HC-blocking peptides-treated ischemic near-term sheep	↑ electroretinography outcome ↓ seizure ↓ status epilepticus ↑ oligodendrocyte and neuronal survival	(O'Carroll *et al.*, 2008, Davidson *et al.*, 2012)
	Astrocyte-specific $Cx43^{fl/fl}$ mice	↓ ATP-induced inflammation ↓ macrophage and microglial recruitment ↑ recovery following spinal cord injury	(Huang *et al.*, 2012)
	Connexin-blocking and Cx37/Cx43 knockdown in bradykinin-induced calcium oscillations in immortalized and primary brain endothelial cells	↓ calcium oscillations	(De Bock *et al.*, 2011)
Heart	LipoxinA4-treated ischemic rats	↓ IL-1β, IL-6, IL-8, TNF-α, and oxidative stress ↑ Cx43 expression ↑ Na^+-K^+-ATPase expression	(Zhao *et al.*, 2013)
	Gap19-treated ischemia/reperfusion in mice	↓ metabolic inhibition-enhanced HC opening ↓ volume overload ↓ cell death	(Wang *et al.*, 2013c)
	Co-culture of murine macrophages and murine atrial myocytes subjected to mechanical stretch, carbenoxolone and apyrase	↓ macrophage migration ↓ increase extracellular ATP	(Oishi *et al.*, 2012)
Blood vessels	Atherosclerotic $Cx37^{-/-}$apolipoproteinE$^{-/-}$ mice	↑ aortic lesions	(Wong *et al.*, 2006, Pfenniger *et al.*, 2015)
	$Cx37^{-/-}$ monocytes or macrophages introduced in hypercholesterolemic $Cx37^{+/+}$ mice	↑ leukocytes in atherosclerotic plaque	(Chanson and Kwak, 2007)
	Polymorphism of Cx37 or blocking of Cx37-based HCs	↓ ATP release	(Chanson and Kwak, 2007)
	Endothelial-specific $Cx40^{-/-}$ mice	Spontaneous atherosclerotic lesions in aorta	(Chadjichristos *et al.*, 2010)
	Atherosclerotic low density lipoprotein $receptor^{-/-}Cx43^{+/-}$ mice	↓ aortic atherosclerosis ↓ atherosclerotic plaques ↓ leukocytes	(Kwak *et al.*, 2003)
Liver	Non-alcoholic steatohepatitic Cx32ΔTg rats	↑ inflammation, oxidative stress	(Sagawa *et al.*, 2015)
	Acetaminophen-treated $Cx32^{-/-}$ mice	No effect on inflammation or oxidative stress	(Maes *et al.*, 2016b)
	Acetaminophen-treated $Cx43^{+/-}$ mice	Tendency of higher cell death, inflammation and oxidative stress	(Maes *et al.*, 2016a)
Skin	Cx43 blocking in wound healing models	↓ wound healing time, inflammation	(Qiu *et al.*, 2003, Mori *et al.*, 2006, Cogliati *et al.*, 2015)

Tissue	Model	Outcome	Reference
	Gap27-treated skin	↑ cell proliferation	(Evans and Leybaert, 2007, Wright *et al.*, 2009, Pollok *et al.*, 2011)
	ACT1-treated chronic venous leg ulcers	↑ fibroblast migration and proliferation ↑ wound reepithelialization	(Ghatnekar *et al.*, 2015)
	αCT1-treated skin	↓ inflammatory response, ↓ area of scar progenitor tissue restoration of dermal structure	(Ongstad *et al.*, 2013)
	$Cx43^{+/-}$ mice	↑ wound healing	(Cogliati *et al.*, 2015)
Kidney	Chronic kidney diseased $Cx43^{+/-}$mice	↓ monocyte infiltration ↓ fibrosis	(Abed *et al.*, 2014b)
	Cx43 antisense-treated chronic kidney diseased mice	↑ renal function	(Abed *et al.*, 2014b)
	Cx43-specific blocking in chronic kidney diseased mice	↓ monocyte adhesion ↓ profibrotic pathways	(Abed *et al.*, 2014b)
Lung	Endothelial-specific $Cx43^{-/-}$ mice	↓ calcium wave propagation	(Parthasarathi *et al.*, 2006)
	LPS-induced lung inflammation in endothelial-specific $Cx43^{-/-}$ mice	↓ neutrophil recruitment	(Sarieddine *et al.*, 2009)
	LPS-treated endothelial-specific $Cx40^{-/-}$ in mice	↑ migration of neutrophils from blood to lungs	(Chadjichristos *et al.*, 2010)
Eye	Cx43 blocking in glaucoma trabeculectomy surgery in rabbit	↓ scarring ↓ Cx43 upregulation	(Deva *et al.*, 2012)
	αa-carboxy terminus 1-treated-rats of corneal inflammation	↓ healing time ↓ inflammation	(Moore *et al.*, 2013)
	Cx43 antisense oligonucleotides-treated cornel scrape wounds	↑ epithelial recovery ↓ oedema ↓ myofibroblast differentiation and proliferation	(Grupcheva *et al.*, 2012)
	α-carboxy terminus 1-treated corneal-wounded rats	↓ healing time ↓ inflammation	(Moore *et al.*, 2013)
	Cx43 antisense oligonucleotides-treated rabit model of glaucoma	↓ myofibroblast production ↓ scarring	(Deva *et al.*, 2012)
	Cx43 antisense oligonucleotides-treated trabeculectomy patients	↓ scarring Long term maintenance of normal intraocular pressure	(Becker *et al.*, 2016)
	Peptide5-treated rat model of retina ischemia/reperfusion	↓ vessel leak ↓ inflammation ↑ neuronal survival	(Chen *et al.*, 2013, Chen *et al.*, 2015)
Immunecells	18β-glycyrrhetinic acid or Cx mimetic peptides-treated human lymphocytes	↓ immunoglobulins M, G and A	(Oviedo-Orta *et al.*, 2001)
	Gap27-treated dendritic cells exposed to IFN-γ and LPS	↓ activation ↓ antigen presentation	(Matsue *et al.*, 2006)
	Activated polymorphonuclear leukocytes from $Cx43^{fl/fl}$	↓ extracellular ATP release	(Eltzschig *et al.*, 2006)
Pancreas	$Cx32^{-/-}$ mice	Acute pancreatitis	(Frossard *et al.*, 2003)
Skeletal muscle	$Cx43^{fl/fl}Cx45^{fl/fl}$ mice	↓ denervation	(Cea *et al.*, 2013)
Bone	Cx43 small interfering RNA-treated arthritic rats	↓ arthritis	(Tsuchida *et al.*, 2013)
	Cx43 small interfering RNA-treated synovial fibroblasts	↓ expression inflammatory genes	(Gupta *et al.*, 2014)