Atherosclerosis is the major cause of death in the Western world. The mechanism leading to atherosclerotic lesion formation has been tremendously updated in the last decades. From a merely degenerative concept, the pathogenesis of the disease is now well ascertained to be inflammatory. It is also recognized that the thrombotic complications of the disease are a consequence of the disruption of the atherosclerotic plaque due to the erosion of the endothelium or the rupture of the fibrous cap covering the lipid core within the plaque (127). The current morbidity and mortality and increasing age of the population require the development of new diagnostic and therapeutic strategies to treat early subclinical disease stages.

In addition to the endothelium, blood vessel walls are composed of many constituents such as matrix base, smooth muscle cells, and pericytes. All these components form a cohesive tissue that requires, for proper function, a constant exchange of information via electrical and chemical signals. A key pathway that allows such communication is gap junction (GJ). GJ channels, composed of six connexins to form a hemichannel in the cell membrane, are important for signaling between intracellular and extracellular spaces. Two hemichannels on adjacent cells can form a full gap channel in the cell membrane, allowing the direct exchange of ions, small metabolites, and other secondary messengers molecules between cell in contact (101).

Pathogenesis of Atherosclerosis

The dysfunction of the endotheium, often induced by hypercholesterolemia and other cardiovascular risk factors, is the initial step of atherosclerosis. Atherosclerotic lesions are typically observed in arteri- nal vessels with high shear stress such as bifurcations. Endothelial cells (ECs), once activated, recruit mainly monocytes and T-cells (46), but also platelets (118). Platelet rolling is initiated by activation-dependent selectins present on endothelial and platelet surfaces (36). Indeed, mice with platelets lacking P-selectin develop smaller atherosclerotic lesions than mice with wild-type platelets (14). This protection is enhanced when both P- and E-selectin are also lacking (30), illustrating the early role of platelets in the disease. Interestingly, the lack of the integrin α5β1 (a subunit of the fibrinogen receptor α5β1) attenuates lesion formation (83). Beside selectins, activated ECs express integrins such as vascular cell-adhesion molecule 1 (VCAM-1) in response to cholesterol accumulation in the intima (23). T-cells and monocytes, expressing both the very late antigen 4 (VLA-4), bind thereafter to endothelium and transmigrate under the influence of chemokines such as macrophage colony-stimulating factor that is produced by low-density lipoprotein (LDL)-stimulated ECs and smooth muscle cells (SMCs) (99). SMCs may also express VCAM-1, promoting further recruitment and retention of mononuclear cells in the intima (72). Once migrated within the plaque, two phenotypes of macrophages appear: inflammatory macrophages and foam cells. The latter cells are characterized by the accumulation of cholesterol in their cytoplasm, resulting from the uptake of oxidized lipoprotein by these cells (113). Besides macrophages, T-cells are the second most important cell population in the atherosclerotic plaque (~10%) (61). They are important determinants in the disease by governing the transition from a latent plaque to a vulnerable plaque (46). CD4+ T-cells and more than an unstabilized lipoprotein 

Rupture of the Atherosclerotic Plaque is the Primary Cause of Sudden Cardiac Death

Acute coronary syndrome (ACS) results mostly of sudden luminal thrombosis (15), which may result from three different pathological processes: plaque rupture, erosion, and calcified nodules (128). Rupture occurs when the fibrous cap overlying a necrotic core is thin and broken, inducing luminal thrombosis. Lesions with erosion may also show a luminal thrombus but are often devoid of necrotic core or the core is isolated from the lumen by a thick fibrous cap (127). Calculated nodules are rarely exposed to trauma, imposing bony core cap with calcium. About 55–60% of ACS are due to rupture, and ~30% of ACS are due to erosion (129). Therefore, plaque rupture is the major trigger of the thrombotic complications of the disease. Interestingly, the rupture of a fibrous cap allows platelets and the coagulation system to enter the vascular system, triggering thrombosis.

Hence, follow-up studies on plaque rupture and myocardial infarction are important to understand the progression of the disease.

Connexin-Based Vascular Wounding

GJs mediate the propagation of electrical and chemical signals, and the cell becomes synchronized for the contraction and relaxation of the vascular wall. In addition, GJs mediate the migration of T-cells by monocytes/macrophages in the plaque through major histo-compatibility antigens II. These T-cells express a pro-inflammatory (TH1) phenotype, suggesting that atherosclerosis is a T1,4-driven pathology (93, 148). T1,4-type cytokines are predominant in plaques, but II, a T1,2-type cytokine, is also produced by a few cells (37). Thus, the initiation of atherosclerotic lesions is induced by many cell types within the vascular wall, circulating or resident. Therefore, the evolution of atherosclerotic plaques is described (11). Thereafter, T-cells express an adhesion molecule called VLA-4 that binds to the very late antigen 4 (VLA-4) on ECs and collagen. However, the subsequent steps of the process are not fully understood. Hence, further studies are required to understand the role of GJs in atherosclerosis.

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Connexins are a family of transmembrane proteins that form gap junctions (GJs), which are channels connecting adjacent cells. GJs allow for the direct exchange of ions, small metabolites, and other molecules between adjacent cells, synchronizing cell responses in tissues necessary for the contraction of cardiac and smooth muscle cells, and possibly for the transmission of signal between neurons and for endothelial repair (65). Specifically, Cx40 is important for blood pressure regulation. Cx40−/− mice are hypertensive (27, 28, 104), possibly due to the requirement of the protein for the transmission of the endothelium-dependent vasodilator response (27). Furthermore, a link between Cx40 expression and renin secretion has been reported. Hence, the plasma titer of renin is increased in Cx40−/− mice due to a modified number and distribution of renin-secreting cells (62).

Connexins in the Vasculature

GJs mediate the direct exchange of ions, small metabolites, and other secondary messenger molecules between adjacent cells (101). This allows for the synchronization of cell responses in tissues, necessary for the contraction of cardiac and smooth muscle cells, for the transmission of signal between neurons and for the organ development. GJs are formed by connexons and more than 20 different connexins have been described (112). Six connexins form a connexon or hemichannel; two connexons form a functional GJ channel. Many combinations of connexins may assemble into channels, and each type of GJ channel has its proper gating and permeability properties. In addition, the expression pattern of connexins is complex with multiple connexins in one cell type, and this is enhanced by the very short half-life of connexins (~1–5 h), indicating that channels are renewed several times daily (101). This signifies that connexins expression modulation at multiple levels could be a mechanism to regulate intercellular cross-talk.

At least four connexins have been described in the vascular system, connecting ECs and SMCs in the blood vessel wall (26, 48, 49). Expression of connexins varies between blood vessel type (48) and species (26). Thus Cx37 and Cx40 are usually expressed in ECs (145), Cx43 and Cx45 are expressed in SMCs. Furthermore, Cx43 is detected in few arterial ECs exposed to turbulent shear stress and in capillaries (22, 38, 119). Cx37 and Cx40 have been observed in SMCs of small elastic or resistance arteries (44, 79, 87, 122). Cx43 is generally considered as the predominant connexin in the media (105). This has been reported mostly for aorta, an elastic artery (105, 122). However, Cx43 can barely be detected in the media of muscular arteries (31) and of coronary arteries (12, 43, 51, 125, 145). Thus many connexins are present in the vasculature, leading to complex communication exchanges within tissue.

Major Roles of Connexins in the Vasculature

Connexins have many functions in vascular physiology, such as conduction of vasomotor responses and tone among SMCs (20, 26, 33), capillary sprouting, and endothelial repair (65). Specifically, Cx40 is important for blood pressure regulation. Cx40−/− mice are hypertensive (27, 28, 104), possibly due to the requirement of the protein for the transmission of the endothelium-dependent vasodilator response (27). Furthermore, a link between Cx40 expression and renin secretion has been reported. Hence, the plasma titer of renin is increased in Cx40−/− mice due to a modified number and distribution of renin-secreting cells (62).

Expression of Connexins by Inflammatory Cells

Atherosclerosis is an inflammatory disease in which immune cells infiltrate the atherosclerotic plaque. These inflammatory cells are mainly blood-borne T-cells and macrophages. They accumulate during the early phases of plaque formation. Adherent murine macrophages are electrically coupled (71), and dye transfer has also been observed between them (82). Interestingly, cellular activation seems to increase GF coupling, as seen in microglia (32) and human monocytes (31). However, other studies have not been able to detect dye transfer between...
human or murine monocytic cells (2, 98), between human mononcytic cells and ECs, and between human mononcytic cells and SMCs (31, 86). Various connexins have been found in mononcytic cells: Cx43 is present in mouse macrophage cell lines (2, 7, 16), in activated peritoneal hamster and mouse macrophages (2, 60), and in mononcytic cells stimulated by tumor necrosis factor (TNF)-α or INF-γ, and Cx43 has been detected in human and mouse monocytes (135).

Lymphocytes form functional GJs. Electrical coupling has been observed after phorbol ester stimulation (56). Dye-coupling between lymphocytes and ECs has also been reported (91). Cx43 is found in human blood-derived T- and B-cells and CD56⁺ (natural killer [NK]) cells (91). Tonsil-derived T- and B-cells express both Cx40 and Cx43 (92). Neutrophils have been shown to express Cx37, Cx40, and Cx43, but not Cx32 (11, 146). After activation by Lipopolysaccharide (LPS) or TNF-α, human neutrophils are able to form morphological, but not dye-coupled, GJs (11). Functional GJs have been shown between ECs and neutrophils, and this was decreased by TNF-α (146). Thus, connexins are expressed and GJ channels are functional in blood cells and reveal a communication network between circulating cells and vascular cells.

Expression of Connexins During Atherosclerosis is Altered and Participates in the Disease Progression

Atherogenesis is a progressive disease, and Cx37, Cx40, and Cx43 expression patterns change during plaque formation (summarized in FIGURE 1) in murine and human atherosclerotic plaques (64). Here, we will report the role of GJs in atherosclerosis throughout the disease progression.

Endothelial dysfunction initiates the disease

The major risk factors for atherosclerosis are aging, hypertension, hyperlipidemia, smoking, and diabetes. These conditions influence endothelium biology. ECs display GJs, and connexin expression is tightly regulated. Deregulation can occur in different pathological conditions that will be discussed here.

Aging seems to induce a general decrease in connexin expression, with Cx40 being relatively undisturbed for a long time (138). Nicotine induces a decrease in Cx43 expression due to an enhanced protein degradation (121). Hypertension is a cause of ECs dysfunction and a major risk factor of atherosclerosis. Hypertensive rats have a reduced endothelial expression of Cx37 and Cx43, but Cx40 expression is not modified (141). Moreover, carvedilol, a commonly used β-blocker for hypertension and cardioprotection, directly upregulates endothelial Cx43 independently of its antioxidant activity (141). Osmotic products of lipoprotein-derived phospholipids upregulate Cx43 and downregulate Cx37 but do not affect Cx40 expression in murine endothelium of carotid arteries both in vivo and in culture (59). ECs are also sensitive to cholesterol titers. Increased GJ assembly between hepatic cells is observed after increasing the cholesterol level or treatment with LDL or apolipoprotein B (85, 86). Besides the effect of cholesterol on Cx43 expression, membrane cholesterol content affects the GJ channels. Indeed, neonatal cardiomyocytes are also protected against the heptanol-induced closure of Cx43 GJs with increased membrane cholesterol (9). Cx37 and Cx40 are abundant in murine endotelium. Although Cx43 is mostly absent in murine aortic endothelium, it is abundant in ECs localized at the downstream edge of the ostia of branching vessels and at flow dividers, regions where the blood flow is turbulent and experienced shear stress (38), but the ECs covering advanced plaques no longer express Cx37 and Cx40 (84,85). These observations have been confirmed by in vitro studies, showing a positive correlation between Cx43 expression and disturbed flow patterns (22, 24, 29). For example, the expression of endothelial Cx43 increases in response to oscillatory shear stress in vitro, but the pressure does not affect Cx43 expression (66). The correlation between coronary heart disease and both Type 1 and Type 2 diabetes mellitus has been recognized by epidemiological data (42, 132). Diabetes mellitus markedly suppresses Cx43 GJs in cardiomyocytes. Interestingly, simvastatin reverses this effect (108). In contrast, endothelial Cx37 and Cx40 are downregulated in diabetic-induced ApoE⁻/⁻ mice, and simvastatin exacerbates the downregulation (53). Coronary ECs of diabetic mice show lowered protein levels of Cx37 and Cx40, but not Cx43, and a reduction of GJ communication (81).

Tissue hypoxia, due to ischemia and the subsequent reoxygenation by pharmacological- or coronary intervention-induced reperfusion increases the production of superoxide that has different biological effect. Hypoxia/reoxygenation of ECs inhibits GJ communication (147). Moreover, abrupt reoxygenation of ECs reduces protein kinase A activity and reduces electrical coupling. This effect is prevented in Cx40⁻/⁻ mice, signifying that the abrupt reoxygenation targets Cx40, compromising arteriolar function (10).

C-reactive protein (CRP) is a conserved protein present in low level in humans. But, in response to infection, cancer, tissue injury, CRP titer increases rapidly up to 1,000-fold (95). CRP is associated with coronary atherosclerotic disease (1, 102) and is a predictive marker for cardiovascular risk (57). It is at present not clear whether CRP is only a risk marker or rather a functional risk mediator (126). Nevertheless, CRP influences the expression of inflammatory mediators in ECs (131). Activated ECs produce chemokines and hemostasis factors by an inflammatory response, which are increased by cholesterol or LPS, and these factors change Cx expression and disrupt GJ channels (136). In contrast, TNF-α decreases Cx43 expression in human ECs (146). C-reactive protein (CRP) is a proinflammatory cytokine (133) that upregulates Cx37 expression and inhibits GJ channel formation against ILF3 (136). Finally, ECs’ response to TNF-α or ILF3 is also influenced by the inflammatory cytokines (117). The regulation of Cx expression in plaques is complex and involves the modulation of both connexin and gap junction expression (19, 103, 146). These changes might be mediated by cholesterol titers. Thus, cholesterol upregulates Cx43 and downregulates Cx37 in ECs (2, 98, 146). As cholesterol is increased in plaques, Cx43 expression is increased and Cx37 expression decreases in plaques.

Leukocytes in atherogenesis

As described a major source of inflammatory cells, leukocytes in atherogenesis. Thus monocytes in atherosclerotic plaque are a rich source of these cells. Monocytes/macrophages and their transformation into foam cells in response to cholesterol and LPS is also a major source of inflammatory cells in atherosclerotic plaques (18, 103, 146). In this context, the migration of leukocytes into the plaques is a critical step in atherogenesis.
The derived phospholipid Cx37 but not Cx43 is expressed in the endothelium (59). Ecs with lowered expression of Cx37 have been observed after cholesterol feeding. Cx37 is expressed in coronary arteries but not in skin vessels and flow is turbulent, but the Ecs express Cx37. Cx43 has been observed in endothelium-derived membrane sacs: tumor necrosis factor decreases the GJ coupling in early passage HUVECs (120). Moreover, epidermal growth factor decreases the GJ coupling in early passage HUVECs (136). In contrast, transforming growth factor (TGF-β) increases Cx43 synthesis (68, 70) but decreases Cx37 expression in Ecs (70). In epithelial cells, TGF-β increases Cx43 expression via p38 and phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathways (116). Finally, basic fibroblast growth factor (bFGF) increases Cx37 expression and GJ communication, and antibodies against bFGF abolish intercellular coupling and decrease Cx43 expression during wound healing (94).

Finally, Ecs are very sensitive to tumor necrosis factor alpha (TNF-α), which activates Ecs by promoting expression of adhesion molecules. Thus treatment of Ecs with TNF-α decreases the expression of Cx37 and Cx40 but does not change Cx43 expression (123). In keratinocytes, TNF-α decreases Cx43 expression, and inhibition of c-Jun N-terminal kinase (JNK) abolishes this expression (117). Activation of Ecs (52, 123) or SMCs (84) with LPS, TNF-α, IL-1α, or IL-1β reduces the GJ communication. Finally, TNF-α induces closure of myoendothelial GJs in co-culture of human ECs and SMCs (54). This modulates both gating and permeability of GJs. Thus a large range of stimuli modify GJ expression and enhance endothelial dysfunction, leading to atherosclerotic initiation.

**Leukocytes infiltrate the arterial intima**

As described above, TNF-α induces changes in expression of connexins in Ecs that affect the migration of leukocytes in different inflammatory pathologies. Thus monocytes and lymphocytes are recruited early in atherosclerosis. A role for connexins in leukocytes migration studied in different inflammatory models and results are conflicting (19, 25). Thus diapedesis of neutrophils is increased or not by using connexin-mimetic peptides or pharmacological channel blockers (19, 103, 146). Using same modulators, monocytes transmigration is decreased (31), but lymphocytes transmigration is only modestly affected (91).

Connexin expression is modulated during atherosclerosis. Endothelial Cx37 and Cx40 expression is considerably reduced in low-density lipoprotein receptor (LDLR)−/− mice on a cholesterol-rich diet for several months (64). Moreover, Cx37 is present in monocytes and macrophages in early and late atheroma (64) but also in medial SMCs beneath advanced atherosclerotic lesions (64).

So, Ecs covering the advanced plaque do not express Cx37 anymore, but this connexin is still expressed on recruited macrophages (64). Atherosclerosis in Cx37−/− ApoE−/− mice under high-cholesterol diet is exacerbated (135) in both descending aorta and aortic sinuses. The transmigration of monocytes is due to the presence of Cx37 on their surfaces and not to the expression of Cx37 on Ecs, as shown by adoptive transfer. Furthermore, the adhesion of monocytes to activated Ecs monolayer is increased when Cx37 is lacking in monocytic cells. The anti-adhesive effect is due to extracellular release of ATP through hemi-channels. Finally, one Cx37 polymorphism in macrophages affects their adhesiveness (135).

Besides Cx37, a specific deletion of Cx40 in Ecs to circumvent the hypertensive phenotype of the systemic Cx40 deletion increases lesion development when atherosclerosis-susceptible ApoE−/− mice were fed with...
During the growing phase, SMCs transmigrate from the media to the intima. There, they continue to grow and produce components of the extracellular matrix, leading to a strong fibrous cap covering the original plaque. In general, this cover safely isolates the plaque from the blood. Macrophages and SMCs filled with lipids die within the plaque and release lipids. This process generates the typical lipid core of atherosclerotic lesions.

At this stage, two qualities of plaque exist. Plaques with a thin cap, prone to rupture, are composed of a large lipid core and numerous macrophages. Their phenotype is dependent on macrophage activity. Macrophage foam cells produce pro-inflammatory cytokines, amplifying inflammatory response that, in turn, induces macrophage proliferation and lipid uptake. Moreover, activated macrophages produce matrix metalloproteinases (MMPs) that degrade extracellular matrix and weaken the fibrous cap.

On the other hand, stable plaques, with larger fibrous cap and reduced lipid core, are less prone to rupture, and thus the stabilization of the plaque has become a potentially new therapeutic goal.

The expression of Cx43 differs in intimal SMCs and depends on the stage of the disease. Its expression is increased at early stage but decreased in advanced human plaques (8). Cx43 expression is also decreased between intimal SMCs in advanced lesions in the human plaques (8). Cx43 expression is also decreased in advanced lesions in the human plaques (8) as well as in LDLR–/– mice (64). In addition, Cx37 appears in medial SMCs beneath advanced atherosclerotic lesions (64). Furthermore, Cx43 mRNA is present in foam cells of human and rabbit atherosclerotic carotid arteries (97). Moreover, Cx43 mRNA is present in foam cells of hypercholesterolemic rabbit (97) as well as in LDLR–/– mice (under cholesterol-rich diet) (18). Altogether, all these results underline the importance of Cx43 communication for and during leukocytes infiltration in atherosclerosis.

**Smooth muscle cell migration in the growing phase**

Finally, Cx43 expression is enhanced in intimal thickening after acute vascular injury (16, 74, 96, 144). Interestingly, the time course of restenosis changes when the Cx43 is reduced (16, 74, 130). Somehow results are opposed, depending on whether the Cx43 expression is systematically reduced, leading to a reduced neointima formation (16), or deleted in SMCs only, leading to an increased neointimal formation (74). It should, however, be kept in mind that the specific deletion of Cx43 in SMCs reduces the expression of Cx43 in aortic endothelium (74), and specific deletion of Cx43 in ECs upregulates Cx43 and a loss of Cx43. Importantly, this platelet-derived growth factor-BB-induced photomorphogenic change is prevented by a reduction of Cx43 expression by an antisense oligonucleotide (17). These findings suggest that Cx43 may also be an attractive target for local delivery strategies aimed at reducing restenosis.

**ConneXins as Cardiovascular Risk Markers and Therapeutic Targets**

There is increasing attention to genetic variation in connexin genes and their relation to cardiovascular disease. A Cx37-1019C polymorphism has been reported to be a potential prognostic marker for carotid atherosclerotic plaque development in a Swedish population (9) and coronary artery disease in a Taiwanese and Swiss population (134, 139). In addition, a Chinese study showed that out of three studied polymorphisms in the Cx37 gene, the C allele contributes to an increased risk of coronary artery disease (48). In contrast, the Cx-10197T polymorphism has been associated with acute myocardial infarction in a Japanese and Sicilian population (50, 77, 78, 137). Finally, the Cx-10197T polymorphism appears in a prospective study of death after acute coronary syn- drome (68). The association of the polymorphism with CAD or MI has not been found in an Irish study group (52). Moreover, the Cx37-10197T polymorphism is not associated with carotid artery or carotid artery mediated disabling stroke in young (68).

Altogether, the role of connexins in their role as atheroprotective molecules is also clearly illustrated in different populations and different atherosclerotic lesions (10). As drug-eluting stents are widely used due to their ability to reduce Cx43 expression (67). Furthermore, the same benefits of Statins, particularly Cx43–/– LDLR–/– mice (67) and Cx40–/– mice (52), have been observed. The polymorphism in the LDLR (123) and platelet-derived growth factor-BB (125) and more cell-to-cell coupling than S-SMCs. Moreover, S-SMCs treated with platelet-derived growth factor-BB acquire an R phenotype, with an increased proliferative, migratory, and proteolytic phenotype and are involved in vascular tissue repair and restenosis. S-SMCs express Cx43, but R-SMCs do not. Moreover, the specific deletion of Cx43 in SMCs reduces the expression of Cx43 in aortic endothelium (74), and specific deletion of Cx43 in ECs upregulates Cx43 and a loss of Cx43. Importantly, this platelet-derived growth factor-BB-induced photomorphogenic change is prevented by a reduction of Cx43 expression by an antisense oligonucleotide (17). These findings suggest that Cx43 may also be an attractive target for local delivery strategies aimed at reducing restenosis.

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intimal thickening (74, 96, 144). Therapy changes have shown results in Cx43 expression to a reduced ICs only, leading to atherosclerosis (74). It should be noted that a low-signature in some vascular tissues may produce toxic effects and be complex. Not to be ignored are the risks of other treatments for atherosclerosis.

In this review, we have summarized an emerging role of connexins in all sorts of cardiovascular disease. Studies on knockout mice have unequivocally demonstrated the role of connexins in atherosclerosis and balloon-induced restenosis. Future challenges not only include the development of specific connexin-targeting drugs for therapeutic applications.

References


Heterogeneity of the gap junction channel function in the immune system.


