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 ascertainment 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 hemicannels on adjacent cells form a full gap junction channel, allowing the direct exchange of ions, small metabolites, and other secondary messenger molecules between cell in contact (101).

**Pathogenesis of Atherosclerosis**

The dysfunction of the endothelium, 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 α₇(α subunit of the fibrinogen receptor α₇(β₃)) 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+ clones of T-cells isolated from atherosclerotic plaques recognize oxidized LDL (114), suggesting a local stimulation of T-cells by monocytes/macrophages in the plaque through major histo-compatibility antigen II. These T-cells express a pro-inflammatory (TH1) phenotype, suggesting that atherosclerosis is a T₄,1-driven pathology (114, 148). T₄,1-type cytokines are predominant in plaques, but IL-4, a T₂,2-type cytokine, is also produced by a few cells (37). Thus the initiation of atherosclerotic lesions is induced by many cell types within the vasculature, circulating or resident.

**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 detected but impose a heavy risk. About 55–60% of plaques are thrombus prone to rupture, and death (129). Therefore, the evolution of ACS depends on the composition of the core, infiltration of foam cells, and the stability of the fibrous cap, is kinetically driven by cell proliferation and cellular matrix remodeling. Interestingly, the fibrous cap, responsible for an unstable plaque, is a complex tissue due to the synthesis and degradation of extracellular matrix proteins secreted by adventitial fibroblasts (39), SMCs (85), and T-cells (25). About 55–60% of plaques are thrombus prone to rupture, and death (129). Therefore, the evolution of ACS depends on the composition of the core, infiltration of foam cells, and the stability of the fibrous cap, is kinetically driven by cell proliferation and cellular matrix remodeling. Interestingly, the fibrous cap, responsible for an unstable plaque, is a complex tissue due to the synthesis and degradation of extracellular matrix proteins secreted by adventitial fibroblasts (39), SMCs (85), and T-cells (25).
nODULES AND FOAM CELLS

Once migrated, macrophages differentiate into foam cells, and monocytes, which are also progenitors of foam cells, and are known to inhibit both collagen production and proliferation of SMCs, the main source of this extracellular matrix (3). Moreover, collagen is degraded by proteases secreted by macrophages, SMCs, and lymphocytes (38, 40, 90). Lastly, the rupture of the fibrous cap allows platelets and leukocytes to be activated by thrombinogenetic tissue factor (TF) in the necrotic core. Interestingly, the main source of TF are monocytes, responsible for the acute thrombus propagation overlying an unstable plaque (41). T-cells also induce the production of TF by macrophages in the plaque (13, 86). Hence, following the formation of the plaque, many cells and processes are responsible for their quality. The plaque rupture is life threatening and leads to thrombosis and myocardial ischemia.

Connexins are Expressed in the Vascular Wall

GJs mediate the direct exchange of ions, small metabolites, and other secondary messenger molecules between adjacent cells (101). This allows for 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 connexins and more than 20 different connexins have 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). Moreover, a polymorphism of Cx40 is linked to an increased risk of hypertension (35). In contrast, it seems that mice with an endothelial-specific deletion of Cx43 suffer from hypotension and bradycardia (73). Although contradictory results have been described as well (119). Interestingly, Cx43 is thought to be involved in the sensitivity to mechanic stimuli due to overexpression during shear stress, in particular in cardiac valves ECs (29, 58).

Deletion of connexins affects also the vasculature development. Indeed, Cx45–/– embryos are infertile (109). Cx37–/– females do not display a noticeable vascular phenotype (34), but when two connexins are lacking, Cx37−/−/Cx40−/− pups die perinatally due to severe vascular abnormalities, characterized by local hemorrhages and sorts of hemorrhagia (110).

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 GJ 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 mononuclear cells and ECs, and between human mononuclear cells and SMCs (31, 98). Various connexins have been found in monocytic cells: Cx43 is present in mouse macrophage cell lines (2, 7, 16), in activated peritoneal hamster and mouse macrophages (2, 60), and in monocytic cells stimulated by tumor necrosis factor (TNF)-α or IFN-γ, and Cx47 has been detected in human and mouse monocytes (135).

Lymphocytes form functional GJs. Electrical coupling has been observed after phorbol 12-myristate 13-acetate 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 (93). Tonofil-derived T- and B-cells express both Cx40 and Cx43 (92). Neutrophils also play a role in atherosclerosis by contributing to the pathogenesis of the disease (83). Neutrophils have been described 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 neutrophils, and this was decreased by TNF-

expression, as Cx43 expression decreased in murine aortic endothelium (147). Moreover, carvedilol, a commonly used β-blocker for hypertension, inhibits GJ communication. This effect is prevented in Cx40–/– mice, and simvastatin exacerbates the downregulation of superoxide that has different biological effect. Hypoxia/reoxygenation of ECs inhibits GJ communication. Finally, ECs of diabetic mice show lowered protein levels of Cx47 and Cx40, but not Cx43, and a reduction of GJ communication (81).

Expression of Connexins During Atherogenesis Is Altered and Participates in the Disease Progression

Atherosclerosis 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 (84). 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. GJs 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). Oxidation 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 cholesterosis. Increased GJ assembly between hepatoma cells is observed after increasing the cholesterosis level or treatment with LDL or apolipoprotein B (85, 86). Besides the effect of cholesterol on Cx43 expression, membrane cholesterol content affects the GJ coupling. This effect is prevented in Cx40–/– mice, and simvastatin exacerbates the downregulation of superoxide that has different biological effect. Hypoxia/reoxygenation of ECs inhibits GJ communication. Finally, ECs of diabetic mice show lowered protein levels of Cx47 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 atherosclerosis 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 activity of the endothelia to ECs (131). Activated ECs release cytokines and chemokines that affect ECs via cytokines. Moreover, CRP is an acute phase response and is upregulated by cytokines, including TNF-α. ECs respond to TNF-α by decreasing Cx40 expression, and this upregulates endothelial Cx43 independently of its antioxidant activity (141). Oxidation 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 cholesterosis. Increased GJ assembly between hepatoma cells is observed after increasing the cholesterosis level or treatment with LDL or apolipoprotein B (85, 86). Besides the effect of cholesterol on Cx43 expression, membrane cholesterol content affects the GJ coupling. This effect is prevented in Cx40–/– mice, and simvastatin exacerbates the downregulation of superoxide that has different biological effect. Hypoxia/reoxygenation of ECs inhibits GJ communication. Finally, ECs of diabetic mice show lowered protein levels of Cx47 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 atherosclerosis 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 activity of the endothelia to ECs (131). Activated ECs release cytokines and chemokines that affect ECs via cytokines. Moreover, CRP is an acute phase response and is upregulated by cytokines, including TNF-α. ECs respond to TNF-α by decreasing Cx40 expression, and this upregulates endothelial Cx43 independently of its antioxidant activity (141). Oxidation 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 cholesterosis. Increased GJ assembly between hepatoma cells is observed after increasing the cholesterosis level or treatment with LDL or apolipoprotein B (85, 86). Besides the effect of cholesterol on Cx43 expression, membrane cholesterol content affects the GJ coupling. This effect is prevented in Cx40–/– mice, and simvastatin exacerbates the downregulation of superoxide that has different biological effect. Hypoxia/reoxygenation of ECs inhibits GJ communication. Finally, ECs of diabetic mice show lowered protein levels of Cx47 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).
Influence of its
derived phos-
tate Cx37 but
endothelium
nature (59). ECs
Increased GJ
observed after
expression with LDL
effect of cho-
nsterol
reduction is a model of rat perit-
also are pro-
expression of Cx37
as well as on the source of
expression factors have an important role in
Cx40–/– mice, induced by cecal ligation and puncture, Cx40 expression increases in aortic ECs (100). In contrast, connexin expression and intercellular communication decrease in murine aortic ECs induced by LPS (111). Apparently, changes in connexin expression depend on the inflammatory model used as well as on the host of infection. Growth factors have an important role in connexin biology. Vascular endothelial growth factor (VEGF) impairs GJ communication in ECs (115). The disruption of Cx43 GJs is due to Cx43 internalization and phosphorylation (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 Cx43 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 Cx37 expression but does not change Cx43 expression (123). In ker-
atticocytes, TNF-α decreases Cx43 expression, and inhibi-
tion of c-Jun N-terminal kinase (JNK) abolishes this expression (117). Activation of ECs (52, 123) or SMCs (84) with LPS, TNF-α, IL-1β, or IL-1β reduces the GJ communica-
tion. Finally, TNF-α induces closure of myoendothe-
ligals in co-culture of human ECs and SMCs (54). This
blocks both gating and permeability of GJs. Thus a large range of stimuli modify GJ expression and enhance endothelial dysfunction, leading to ath-
erosclerosis initiation.

**Leukocytes infiltrate the arterial intima**

As described above, TNF-α induces changes in expres-
sion of connexins in ECs that affect the migration of leukocytes in different inflammatory pathways. 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 atheroscle-
rosis. Endothelial Cx37 and Cx40 expression is consid-
erably 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 atheroscler-
oses (64) but also in medial SMCs beneath advanced atheroscle-
rotic 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 mononuclear cells is due to the presence of Cx37 on their surfaces and not to the expression of Cx37 on ECs, as shown by adoptive trans-
fer. Furthermore, the adhesion of mononuclear cells to activated ECs monolayer is increased when Cx37 expression is lacking in mononuclear cells. The anti-adhesive effect is due to extracellular release of ATP through hemi-
channel. Finally, one Cx37 polymorphism in macrophages affects their adherence (135).

Besides Cx37, a specific deletion of Cx40 in ECs to cir-
cumvent the hypertensive phenotype of the systemic Cx40 deletion increases lesion development when ath-
erosclerosis-susceptible ApoE–/– mice were fed with

**Physiology**  •  Volume 24  •  February 2009  •  www.physiologyonline.org

---

**Figure 1** Connexins are differentially expressed during atherosclerotic plaque formation

Connexin expression is represented by the cellular compartment. When connexins are expressed in a particular area within the tissue, they are represented in color.

---

**Figure 2** Disease progression

The leftmost panel represents the blood vessel in the normal state. The last stage represents the blood vessel after balloononing with the optional use of stent, leading to neointima formation. Stars signify an expression within the neointima.
high-cholesterol diet (18). Altogether, all these results underline the importance of GJ communication for and during leukocyte infiltration in atherosclerosis.

Smooth muscle cell migration in the growing phase

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. Macrophage 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 extra-cellular 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 hypercholesterolemic rabbit (97) as well as in LDLR−/− mice (64). In addition, Cx37 is present in medial SMCs beneath advanced atherosclerotic lesions (64). Furthermore, Cx43 mRNA is present in foam cells of human and rabbit atherosclerotic carotid arteries (97, 98). The reduction of Cx43 expression inhibits the formation of atherosclerotic lesions in mice models. Cx37+/− LDLR−/− mice (under cholesterol-rich diet) display reduced atherosclerosis lesions, with smaller lipid cores and fewer macrophages and T-cells despite normal leukocyte blood counts (67). In addition, lesions have thicker fibrous caps containing more SMCs and interstitial collagen. Interestingly, activation of monocyctic cells, which are associated with the release of MMP-2 and -3, increases GJ communication through Cx43 channel (31). Enhanced MMP release may favor plaque rupture. Interestingly, Tα1 cα3β1 cells secrete more MMPs than Tα1 cα4β1 (6). Moreover, both Cx43 expression and dye-coupling between macrophages and T-cells increase in Tα1 cα4β1 cells compared with Tα1 cα3β1 (98), pointing out a potent role of connexins in atherosclerotic plaque quality. Thus Cx43 targeting potentially favors plaque stabilization besides its action on plaque development (133).

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, 139). 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 neointima 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 reduces Cx43-coding mRNA in the adjacent vascular smooth muscle layer (73). This reflects the complex GJ interactions between different cell types. Similar interactions are observed in Cx40−/− mice, supporting a tight relationship between different connexins in ECs.

Recently, it has been described that SMCs of pig coronary arteries show a heterogeneous phenotype, with both spindle-shaped SMCs (S-SMCs) and thomboïd SMCs (R-SMCs) (47). S-SMCs are predominant in the normal media, whereas R-SMCs are present in stent-induced intimal thickening. R-SMCs have an increased proliferative, migratory, and proteolytic phenotype and are involved in vascular tissue repair and restenosis. S-SMCs express Cx40, but R-SMCs do not. S-SMCs display higher Cx43 expression levels 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 upregulation of Cx40 and a loss of Cx43. Importantly, this platelet-derived growth factor-BB-induced phenotypic 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 Cx37-1019CT polymorphism has been associated with acute myocardial infarction in a Japanese and Sicilian population (50, 77, 78, 137). Finally, the Cx-1019T polymorphism appears in a prospective study of death after acute coronary syndrome (68). The association of the polymorphism with CAD or MI has not been found in an Irish study group (52). Moreover, the Cx37-1019T polymorphism is not associated with CAD or MI and has been linked to hypertensive disorder (6). Altogether, the use of connexins in their role as drug-eluting stent markers is also clearly illustrated by recent studies from the Statin (HMG-CoA reductase) treatment of atherosclerosis model (49) used due to its cholesterol-reducing effects (90). Interestingly, Statins also increase Cx43 expression in human carotid artery (141). GJ communication between cell types has also been studied as an important factor to the lipid-lowering effect of Statins and other lipid-lowering agents (126). Furthermore, a recent study showed the same benefit of calcium channel blockers on decreasing atherosclerosis in Cx37−/− mice (67). Furthermore, a recent study also showed a decrease of enoximone-stimulated HMG-CoA reductase in porcine models (142). The findings underline the importance of GJ and the role of Statins in atherosclerosis.

Along with the above findings, the role of connexins as drug-eluting stent markers is also considered as a potential risk factor for the development of atherosclerosis (143, 149). Carotid atherosclerotic models induced in porcine and human media first an inflammatory response of the media that is followed by a porcine model, which is followed by neointima formation (17). A novel approach is the use of local delivery strategies for improving healing, expression of connexins, and the role of Statins. These studies show that the use of Statins in atherosclerotic plaques is also clearly illustrated by recent studies from the Statin (HMG-CoA reductase) treatment of atherosclerosis model (49) used due to its cholesterol-reducing effects (90). Interestingly, Statins also increase Cx43 expression in human carotid artery (141). GJ communication between cell types has also been studied as an important factor to the lipid-lowering effect of Statins and other lipid-lowering agents (126). Furthermore, a recent study showed the same benefit of calcium channel blockers on decreasing atherosclerosis in Cx37−/− mice (67). Furthermore, a recent study also showed a decrease of enoximone-stimulated HMG-CoA reductase in porcine models (142). The findings underline the importance of GJ and the role of Statins in atherosclerosis.
intimal thickening (74, 96, 144). Loss of connexin expression results in changes in coronary phenotype (17). Cx43 expression is lost in atherosclerotic lesions (21). Cx40 has been linked to hypertension in men (35).

Altogether, these data demonstrate the importance of connexins in atherosclerosis and hypertension and their role as potential prognostic markers. However, it also clearly illustrates the need for studies in larger populations and for well defined clinical end-points.

Stains (inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase [HMG-CoA reductase]) belong to the cornerstone treatment of atherosclerotic disease and are widely used due to their efficacy in lowering plasma cholesterol, reducing atherosclerosis-related morbidity and mortality (124). Moreover, stains have multiple pleiotropic effects that modulate atherogenesis independently on their mechanism on lipids (76, 86). Stains also inhibited, in a dose-dependent manner, Cx43 expression in human vascular cells and reduced GJ communication within the prescribed pharmacological range (133). The pleiotropic role of stains has also been studied in mice. Indeed, mice are resistant to the lipid-lowering effect of stains, allowing the discrimination between pleiotropic and cholesterol-lowering effects in plaque stability (75). Hence, stains reduce Cx43 expressions in plaques of LDLR–/– mice (67). Furthermore, these stain-treated mice display same beneficial plaque quality changes as Cx43+/+ mice (67). Moreover, stains reverse the decrease of endothelial Cx43 after long-term lipid-rich diet (142). Thus stains appear as potent connexins modulators, a mechanism that could synergize with its lipid-lowering effect to reduce atherosclerosis mortality.

Along with medical therapy, mechanical intervention on arteries is often necessary. Despite new techniques in percutaneous coronary intervention, such as drug-eluting stents (DES), arterial occlusion caused by neointimal hyperplasia (in-stent restenosis) or thrombosis remain an important problem (89). Carotid balloon distension injury in animal models induces marked endothelial denudation, leukocyte infiltration, and activation of medial SMCs. In a rat model of balloon acute injury, an increased expression of Cx43 is measured in SMCs within the media first and later in the neointima as well (144). In a postice model, Cx40 is downregulated and Cx43 is markedly upregulated in stent-induced intimal thickening (17). After denudation injury and 28 days of healing, expression of Cx40 returns to that of controls, while expression of Cx31 and Cx43 is increased compared with controls (140). Furthermore, a decreased macropage infiltration is observed in LDLR–/– mice with reduced Cx43 expression (Cx43+/+ mice) 7 days after balloon injury, and Cx43+/+ LDLR–/– peritoneal macrophages display a decreased chemoattractant activity for SMCs. In addition, SMC infiltration and proliferation is not associated with carotid artery intima-media thickness, carotid artery compliance, or brachial artery flow-mediated dilatation (all markers of subclinical atherosclerotic disease) in young Finns adults (21). Cx40 has been linked to hypertension in men (35).

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. Possible targets now include the development of specific connexin-targeting drugs for therapeutic applications.

**References**


4. Angelillo-Scherrer A, Roth I, Sugeng LI, Doolen D, Channon K, Weidmann P. Decreased expression of von Willebrand factor, endothelial nitric synthase (eNOS), and Cx43, suggesting endothelial dysfunction (143).


REVIEWS


The page contains a list of references formatted in a specific style. Here is the extracted text in a plain text format:


