



Connexins and intercellular communication in arterial growth and remodeling

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Abstract

Gap junction functionality and intercellular exchange of chemical messengers and other biologically important cellular signals makes communication between adjacent cells possible and is essential for multicellular living systems. This intercellular communication is carried out through gap junction channels that are comprised of multimeric connexin (Cx) proteins and that provide physical linkages between neighboring cells. This Cx-specific gap junction intercellular communication (GJIC) helps perform numerous essential physiological functions in different organ systems. In vascular tissues, reciprocal GJIC between intimal vascular endothelial cells (VECs) and medial vascular smooth muscle cells (VSMCs) helps to control blood flow and arterial pressures by signaling contraction or relaxation events. In the vascular system appropriate GJIC also regulates responses to circulating hormones and other vasoactive factors as well as growth during episodes of stimulated angiogenesis and/or vasculogenesis. Deleterious GJIC, however, serves as a contributing element in vascular pathologies and plays key roles in abnormal vascular cell proliferation, migration, and inflammation, foundational mechanisms of arterial remodeling and neointima development. In this review we discuss the critical roles of vascular gap junction Cx proteins and GJIC in regulating pathologic arterial remodeling.

Keywords: Atherosclerosis, connexins, gap junction intercellular communication, inflammation, migration, neointima, pathology, proliferation, vascular remodeling

Introduction

Biological systems are naturally dynamic, and appropriate cell-to-cell communication is necessary for normal physiological functions and in order to maintain homeostasis in an intact living system. Many body functions such as sinus rhythm and cardiac conduction, vascular myogenic tone, skeletal muscle coordination, intestinal movement and motility, and many forms of neuronal transmission require constant communication between cells in order to optimally perform. Specific channels known as gap junctions exist between cells for this transfer of messenger molecules and/or ions through gap junction intercellular communication (GJIC). In the cardiovascular system, disturbances in the expression of gap junction proteins (connexins) and/or functional changes via GJIC have been shown to cause or promote certain disorders such as arrhythmia, diabetes, cardiomyopathy, atherosclerosis and vascular occlusive disorders. In this regard, studies have attempted to fully understand the physiological regulation of and inflammatory

mediators involved in cell-to-cell communication and GJIC during atherosclerosis and vascular remodeling. This review article describes the essential roles of gap junction proteins and GJIC in vascular pathology and their significance as potential therapeutic targets in the vascular system.

Review

Connexins and intercellular communication

The concept of intercellular communication and its role in the control of cell growth was originally put forth in 1979 by Loewenstein [1,2]. Living systems are active, and a constant exchange and interplay of various components between cells and within tissues is necessary in order to maintain a living state. In multicellular organisms, communication between cells plays a critical role in the ability of the tissues to adequately perform their functions. This intercellular communication is vital to maintain normal bodily functions, and in cardiovascular tissues GJIC is involved in many critical processes such as cell differentiation, growth

control, determination and control of vasomotor tone, and coordination of contraction and conduction of cardiac muscle cells [3-5].

The special transmembrane channels that facilitate intercellular communication are known as gap junctions. Gap junctions are comprised of specific transmembrane proteins called connexins (Cx) [6,7] which make up a family of structurally-related elements that exist as different types varying with respect to their tissue distribution and molecular weights. About 21 different types of Cx's have been identified in humans [8] and these vary with respect to cellular localization and physiological functions. Cx monomers combine to form hexameric hemichannels called connexons that can associate with connexons on adjacent cells to form integrated and communicative gap junctions that allow the intercellular passage of ions and small molecules via GJIC. Depending on tissue and cell type the gap junction channel can be made up of the same (homomeric) or different (heteromeric) connexin types, and these have different capacities to operate as cell-to-cell channels in context-specific fashion.

Connexins in vascular physiology

In the cardiovascular system, GJIC has many functions in normal vessel physiology and maintenance and is also intimately involved during pathophysiological disorders. In VECs and VSMCs, GJIC regulates intercellular ionic coupling and coordinates vascular cell responses to external, paracrine and autocrine stimuli. The transverse and longitudinal signaling regulated by GJIC in vascular beds uniquely allows cellular and often directed exchange of second messengers, metabolites and ions between VECs and VSMCs and maintains normal vascular myogenic tone and tissue function [4,5,9]. For example, vasoconstriction from acetylcholine is an integral aspect of the bidirectional cellular communication performed by gap junctions [10]. Additionally, GJIC is important in maintaining cell quiescence [11], endothelial repair [12], and for capillary sprouting that occurs during angiogenesis. An important role played by Cx40 is in the maintenance of arterial blood pressure [13]. At least four different types of connexins have been reported in VECs and VSMCs [14,15], and with developments in molecular biology it has been found that Cx43 is more abundant in VSMCs while Cx40 is more abundant in VECs [16], adding to the context-specificity of Cx biology in vascular tissues. The other reported Cx types present in the vasculature are Cx37 and Cx45 [17-19]. In vascular cells Cx43 monomers combine to form hexameric hemichannels that form gap junctions to allow the intercellular passage of ions and small molecules (less than 1 kDa) such as Ca^{++} , ATP and cyclic AMP [20]. A number of studies have related impairment of Cx37, Cx40, Cx43 and/or Cx45 with vascular abnormalities in genetically-deficient mice [21-24]. In fact, some of the Cx43 deletions are lethal and the embryos do not survive [25], demonstrating an essential role of Cx and GJIC in normal tissue function and viability.

Atherosclerotic vascular disease

Atherosclerosis is the major cause of death in Americans and globally, and its prevalence continues to increase in developing countries. In recent decades, a plethora of information has been obtained regarding mechanisms leading to the initiation, evolution and complication of atherosclerotic lesions. Dysfunction of the vascular endothelium is induced by hypercholesterolemia or other cardiovascular risk factors and is considered the initiating step in the formation of an atherosclerotic plaque. The activated endothelial cells then engage monocytes, T-cells [26] and platelets [27] in the evolution of plaque formation. Several inflammatory mediators also actively participate in the growth of the plaque that ultimately leads to complication with vascular occlusion and subsequent ischemia of downstream tissue. The complications of the disease are basically due to the disruption of the atherosclerotic plaque caused by the erosion of the endothelium and/or rupture of the fibrous cap covering the lipid core [28]. The broken plaque may then embolize to downstream vital organs leading to localized cardiac ischemia, cerebral stroke and/or peripheral vascular obstruction.

Following unsuccessful lifestyle modification (to reduce cardiovascular risk) and/or pharmacologic therapy, vascular intervention such as balloon angioplasty and/or bypass grafting is often employed as a surgical approach to combat vascular occlusion. Unfortunately, iatrogenic stenosis following intervention often occurs, and this is usually described as hypertrophic wound healing [29] and mainly involves two processes: neointimal formation and constrictive remodeling of the vessel wall. The hypertrophic wound healing process begins with the removal of the endothelial layer during balloon expansion and vessel wall dilation. The endothelial layer is antithrombogenic in nature. During vascular intervention, endothelial denudation and medial tearing disrupts this protective lining and creates a pro-thrombogenic environment with exposure of the circulating blood cells to the sub-endothelial matrix that contains numerous platelet-activating factors such as thrombin, thromboxane, platelet-activating factor and collagen. The generation of thrombin stimulates additional platelet activation [30]. The formed thrombus contains chemotactic and mitogenic factors that serve as a matrix for the migration and proliferation of medial and sometimes adventitial VSMCs [31]. Cytokines and growth factors released from the activated platelets and macrophages contribute to this phenotypic modulation of VSMCs and subsequent migratory and proliferative activities. The transformed VSMCs migrate towards the source of stimulation and start to proliferate, in turn, producing a stenotic neointima. The neointima is then further developed by excessive matrix synthesis and the accumulation of other types of cells such as circulating progenitor cells and myofibroblasts originating from the adventitia [32,33]. During this process there is also a gradual loss of the contractile phenotype of the cells in the tunica media and loss of contractile function of the blood

vessel. Formation of the neointima is followed by inward remodeling of the vascular architecture [34]. Gap junctions play important roles between resident VECs and VSMCs and circulating cells during this vast array of cellular changes in atherogenesis as these components need to communicate with each other in order to result in an aggressive and effective pathological manifestation.

Vascular connexins and inflammation

As complement to this induction of expression of Cx's and GJIC during atherogenesis, Cx's have been found in several types of circulating inflammatory cells such as macrophages, [35,36] microglia [37] and monocytes [38]. Functional GJIC has also been observed to occur between isolated blood platelets [39]. Following treatment with tumor necrosis factor (TNF)- α or IFN- γ , these monocytic cells stimulate the expression of Cx43 while neutrophils have been reported to express Cx37, Cx40, and Cx43 [40,41]. Thus, both circulating and vessel wall cells express Cx's and have functional gap junction channels, revealing a vital communication network between stationary cells of tissues and circulating cells. Following balloon angioplasty or stenting, a number of inflammatory mediators are released along with the stimulation of macrophages and other inflammatory cells. A well known marker for inflammation, the C-reactive protein (CRP), increases up to 1,000-fold after tissue injury or in response to infection and cancers [42]. CRP also influences the gene expression profile of human VECs and enhances monocyte adhesion to VECs. Additionally CRP has been reported to upregulate Cx43 mRNA expression [43]. Thus connexin expression and GJIC may be altered in inflammation and can be considered to have a role to play in neointimal growth and atherosclerosis.

Inflammation is an inherent component of atherogenesis [44]. As the plaque develops at the endothelial layer it down-regulates local VEC and VSMC Cx's and disrupts GJIC [45]. In human umbilical venous endothelial cells (HUVECs) that express Cx32 and Cx40 as well as Cx43, treatment with TNF- α decreased Cx32 mRNA expression and protein, where as this was not observed after treatment with lipopolysaccharide (LPS) or interleukin (IL)-1 β [46]. In contrast, leukocytes upon treatment with LPS induced Cx43 which formed junctions with the endothelial cells [47]. Thus the type of Cx and tissue involved decides the fate of Cx modulation during vascular disease. In atherosclerotic plaques, the pattern of Cx expression is altered and is not similar to that observed in normal, non-diseased vascular tissue. The endothelia of non-diseased aortas express Cx37 and Cx40 where as in the media Cx43 is present. As an atheroma advances, the presence of Cx37 and Cx40 is also observed in the medial VSMCs and in the macrophages in the lipid core but not in the endothelium covering the plaque. Alternatively Cx43 is also observed in the endothelia at the ends of the plaques and in fewer quantities than found in neointimal cells [48].

Connexins, intercellular communication and neointimal growth

The first correlation between atherosclerotic vascular disease and Cx43/GJIC in VSM was described in 1995 by Blackburn et al. [49]. In atherosclerotic plaques the phenotype of the cells is changed and leads to the formation of foam cells. In normal vessels Cx43 is located more towards the adventitia [50], but in atherosclerosis, increased Cx43 levels were observed in the VSMC's compared to foam cells. Later, this group also reported increased VSMC Cx43 levels in the neointima after vascular injury [50]. In this study, Cx43 expression was upregulated in both the medial and intimal cells yet with more gap junctions in the intima than the media. The Cx43 levels were also higher particularly in the neointima. Vascular remodeling after carotid artery injury is primarily due to the migration and proliferation of VSMCs, unlike atherosclerosis which is largely due to leukocyte infiltration [50]. Inflammation is observed in both conditions—primary atherosclerosis and complications following balloon angioplasty. VSMCs in normal blood vessels are of the contractile phenotype which is an important characteristic of healthy vasculature [51]. Prior to the use of experimental atherosclerotic or carotid injury models, in an *in vitro* study a change in the phenotype from contractile to synthetic leads to upregulation of Cx43 in VSMC's [52]. The synthetic cells express a number of growth factor receptors that may have a role in modulating Cx expression [53]. The presence of Cx43 anti-sense or Cx43 blocking peptides has been reported to reduce platelet-derived growth factor (PDGF)-BB-induced migration of VSMC's. The Cx43 anti-sense also prevents the PDGF-BB-induced phenotypic changes of porcine VSMCs [5]. These findings suggest that expression of Cx43 and its function play important roles in the control of VSMC migration.

The progression of restenosis after vascular surgery may also be influenced by thrombosis at the site of the injury. Indeed, increased platelet activation at the site of the injury results in increased PDGF-BB secretion, which then has additional growth-promoting effects on VSMCs [5]. Unfortunately the impact of platelet Cx37 in this pathology has not yet been investigated. Studies of Cx as modulators of migration or proliferation suggest that they may play roles in these cell-to-cell and/or platelet-to-cell processes via either channel dependent (hemichannel or gap junction channel) or channel independent interactions with cytoskeletal proteins, enzymes or junctional proteins [54,55].

There have been conflicting reports on the role of Cx43 in neointimal growth and vessel wall remodeling. While some studies suggest that reducing Cx43 limits neointimal formation, thereby implicating Cx43 as a positive inducer of vascular remodeling, others have reported that knocking out Cx43 enhances neointimal formation, thereby suggesting growth-inhibitory capacity of Cx43 in the vasculature [4,56,57]. The context and experimental conditions of these studies differ greatly and these results have to be compared carefully

in order to have a better insight into the exact roles of Cx43. Hypercholesterolemic mice with partial Cx43 ablation (Cx43^{+/-}/LDLR^{-/-}) demonstrate reduced neointimal formation compared to mice with normal expression of Cx43 (Cx43^{+/+}/LDLR^{-/-}) [56]. These findings agree with earlier reports [4,50,58] which showed that vascular injury increases Cx43 expression, and so approaches to limit Cx43 expression could lead to a reduction in neointimal growth and prove beneficial. However, these results were dramatically opposite when a complete knockout of Cx43 in VSMCs was used [4]. Here the authors expected a complete deletion of Cx43 in almost all SMC systems, but mosaic Cx43 expression was still evident in the media of the KO mice. The authors felt that this could have been due to an incomplete gene deletion when using the Cre system, and in turn residual Cx43 still remains in the vascular media, although it can be considered to be less than the Cx43 present in Cx43^{+/-}/LDLR^{-/-} mice. Some other reasons for these two contrasting results could be differences in the models and animals used, but it does not negate an important role for Cx43 in neointimal growth and cannot be simply labeled as different vascular adaptive processes. Some additional reasons could be the differential, context-specific roles of Cx's in the regulation of cell proliferation and growth.

In injury-induced vessel remodeling, reduction of Cx43 functionality using a pharmacological modulator carbenoxolone reduced neointimal growth while using a small interfering RNA (siRNA) against Cx43 reduced VSMC proliferation *in vitro* [57]. This study and other studies to date mostly report the effects on Cx43 expression and/or localization but generally do not fully address the effects of Cx43 and GJIC functionality. Thus it is not clear if this increased expression of Cx43 actually causes an increase in GJIC *in vivo* and if abnormal GJIC is indeed the key mediator of these pathological processes (versus Cx expression only).

A similar result could relate to a decrease in Cx expression and neointimal formation when the species under study is changed. It has been reported that balloon injury induces Cx40 mRNA and protein expression in neointimal VSMCs in the New Zealand white rabbits [59,60]. In other studies in the presence of statins, known to possess anti-inflammatory and anti-proliferative properties, the formation of the neointima induced by balloon injury is reduced along with a decrease in the expression of Cx43 and Cx40 at the site of injury [59]. Similarly, the angiotensin-converting enzyme inhibitor ramipril has been effective in inhibiting neointimal formation after balloon injury along with the down-regulation of Cx43 mRNA and protein [60] in New Zealand white rabbits. One other study, although not directly involving vascular injury, has suggested that inducing hypercholesterolemia in rabbits reduces the levels of Cx43 in the VSMC's of rabbits compared to their normal counterparts [61]. This observation could indirectly refer to a change in cellular phenotype due to alteration in normal Cx43 levels in VSMCs in the presence of increased cholesterol levels.

The turnover of Cx proteins is relatively fast with half-lives ranging from 1 to 5 h [8]. The protein expression of Cx's as well as functional GJIC may be controlled differently by chemokines that stimulate cell growth. In our recent study aimed at understanding the regulation of Cx43 expression and functionality with respect to VSMC growth in the presence of cyclic nucleotides [62], we observed that although both cyclic AMP and cyclic GMP increased Cx43 expression, only the agonist 8Br-cyclic AMP increased GJIC and at the same time was effective in reducing VSMC growth, suggesting that a closer relationship exists between vascular cell proliferation and GJIC than between vascular growth and Cx protein expression alone. The increase in the levels of Cx43 has been observed as early as the 1st day after vascular injury in the media on the luminal side [50] and this increase is maintained even in the fully developed neointima. The reason for this increase in Cx43 could be related to the release of prothrombotic factors such as thrombin by the endothelium after injury. Thrombin has been shown to stimulate Cx43 expression in cultured VSMC's [63,64]. Secondly, the neointimal cells are phenotypically altered, growing in response to an injury that could release growth factors that enhance Cx expression and self-stimulate [63-65]. The VSMC cell line A7r5 is obtained after modifying embryonic rat thoracic aortic VSMCs, and gap junction permeability is reduced in these proliferating cells [67]. Changes in the cellular phenotype have been shown to reduce gap junction communication; thus, this decrease could be a stimulating factor to increase the turnover rate of Cx43. Decreased GJIC may lead to negative feedback with respect to intercellular communication via the Cx's stimulating the increase in Cx43 expression in response to the altered rapidly proliferating neointimal cells or synthetic cells than the normal tissue.

Following vascular injury in the carotid artery, local VSMCs respond by initially replicating in the media and later by migrating to the neointima and subsequently proliferating there [44,68]. Proliferation and migration are separate events yet share common mechanistic foundations. Some subpopulations of cells may proliferate in the media before migrating while others may migrate directly, without proliferating initially [45,69]. In order to migrate, it is important that cells shed their links with their neighbors and in the process lose their cell-to-cell contacts including gap junctions. The loss of gap junctions in a number of cell types has been associated with cell division [46,70]; thus, reduced GJIC has been widely linked to rapid proliferation and uncontrolled growth. Some cancer cells have been reported to show gap junction loss compared to non-cancerous tissues, and the transfection of Cx's into transformed cells has been reported to restore GJIC and suppress tumor growth in nude mice [7]. From this background, lack of gap junctions might be expected to typify the synthetic state of VSMCs during rapid growth.

Conclusions and future directions

This article presents a brief overview of the role of Cx's and

GJIC in the multifaceted pathology of vascular remodeling. Up until around 2009, there was considerable interest in the genetic and/or molecular modulation of Cx43 expression in cardiovascular and other body systems. More recently, though, the focus of many studies has been in the pharmacological modulation of Cx43 expression and function. Connexins and GJIC are vital to normal physiological functions, and the therapeutic value of manipulating Cx expression and/or GJIC is clear; however, there is clear separation between expression and function in terms of Cx biology and its impact on cardiovascular tissues. The principal hurdle is the differential regulation of Cx's and their GJIC which is most likely context-specific and largely dependent on local metabolic and physiological status. Another major limitation lies in the experimental models available with which to conduct experiments to study active GJIC. Cellular communication is an extremely dynamic process, and to date only several experimental approaches exist (including FRAP, Lucifer yellow transfer, and dye microinjection) that are available for basic and clinical scientists. Primarily, studies are needed to address the time-dependent role and interplay of inflammation and growth with cellular communication after vascular injury. Although a few studies have defined time-dependent Cx expression after vascular disease or injury, whether this increased expression affects GJIC and overall gap junction biology is unknown. Increasing our understanding with respect to the roles of vascular cell connexins and their functionality in vessel disease, injury and inflammation is essential for new and exciting developments in the field.

List of abbreviations

Cx: Connexin
GJIC: Gap junction intercellular communication
VEC: Vascular endothelial cell
VSMC: Vascular smooth muscle cell
LDLR: Low density lipoprotein receptor
PDGF: Platelet-derived growth factor
HUVEC: Human umbilical venous endothelial cells

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Authors' contributions	CNJ	DAT
Research concept and design	✓	--
Collection and/or assembly of data	✓	--
Data analysis and interpretation	✓	✓
Writing the article	✓	✓
Critical revision of the article	✓	✓
Final approval of article	✓	✓
Statistical analysis	--	--

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