International Journal of
Biological Studies
(IJBS)

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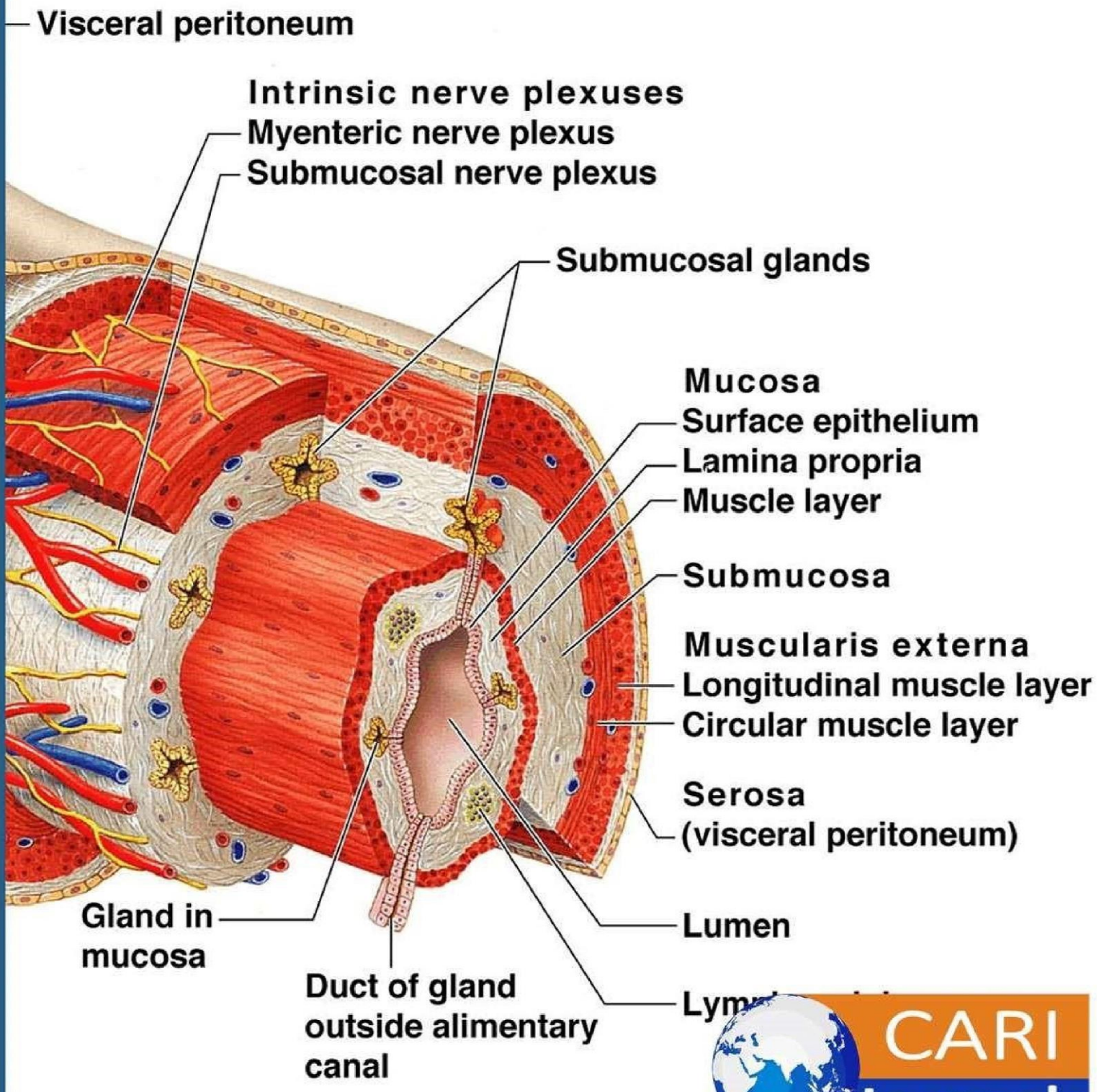

CARI Journals

International Journal of Biological Studies
ISSN: 2957-7764 (Online)
Vol. 4, Issue No.1, pp 62 - 79, 2024
www.carijournals.org

Gap Junctions formed by Connexin 43: from Normal Function to Physiological Impact in its Change in the Cardiovascular System

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Accepted: 18th Sep, 2024, Received in Revised Form: 19th Oct, 2024, Published: 22nd Nov, 2024

ABSTRACT:

Purpose: This study highlights the role of gap junctions that allow communication between adjacent cells and in the cardiovascular system, with the most abundant isoform being connexin 43, providing the basis for intercellular communication, allowing the transfer of small molecules and the propagation of calcium waves in cardiomyocytes. This review aims to provide the main information on the role of connexin 43 in the cardiovascular system and to address the pathologies associated with its alteration.

Methodology: a search was carried out in the databases of the CAPES journal portal, *Scielo, Scopus, Science Direct* and *PubMed* using keywords and selecting the articles with the inclusion and exclusion criteria to structure a work aimed at students and researchers in the areas of cell biology, biophysics and physiology.

Findings: This study investigated the functional and structural anomalies of Cx43 in cardiac pathologies, highlighting that the lateralization of this protein is a recurrent event in several cardiovascular diseases, often associated with dysfunctions in the rhythms and electrical conduction of the heart. Furthermore, the role of Cx43 in mitochondria was analyzed, a recently recognized aspect that has aroused increasing interest. The results indicate that alterations in Cx43 may represent a promising therapeutic target, offering new perspectives for the development of clinical disciplines in cardiac diseases.

Unique contribution to theory, practice and policy: A consolidated analysis of the demonstrated evidence suggests that gap junctions, composed of different isoforms of connections, play an essential role in the transmission of the cardiac electrical impulse. From these findings, it can be inferred that both genetic diseases and acquired pathologies are associated with modifications in the levels and subcellular distribution of connexin. Changes in the expression and positioning of these proteins can therefore trigger the worsening of pathological conditions, compromising cardiac function and enhancing the development of electrical conduction dysfunctions. In this context, connections emerge as promising targets for the development of therapeutic strategies, offering new perspectives for the treatment of a wide range of cardiac diseases.

Keywords: *Gap junction, Connexin 43, Cardiovascular System*

1) INTRODUCTION

Among the various forms of intercellular communication, we highlight the one that allows direct communication between cells and this occurs through gap junctions, characterized by transmembrane channels that enable bidirectional communication in the tissues (Dhein, 1998).

Connexins 40, 43 and 45, as well as other gap junctions, allow the exchange of information and metabolites between adjacent cells, which are essential for the maintenance of tissue homeostasis (Flagg-Newton *et al*., 1979; Hervé *et al*., 2004; Zhang; Wang and Chen, 2023). Among them, connexin 43 is widely expressed in various tissues and organs, being the most abundant in the body, which gives it great scientific relevance (Leithe; Mesnil and Aasen, 2018).

Several studies have demonstrated the fundamental importance of gap junctions for maintaining the homeostasis of the organism in which they are present (Neijssen *et al*., 2005), including mobile cells of the immune system (Fortes *et al*., 2004; De Carvalho *et al*., 2021).

In tissues, the functions of connexins vary according to the role played by the tissue in the body and the cell type that composes it, participating in processes such as: the homeostasis of various tissues; the mediation of inflammatory processes; tissue repair; hematopoiesis; insulin secretion by pancreatic beta cells; coordination of calcium wave propagation in heart tissue cells; contribution to cardiovascular and neural activity, regulation of carcinogenic factors, among others (Cao *et al*., 1997; Chanson *et al*., 2005; Kar *et al*., 2012).

Intercellular communication mediated by gap junctions formed by Connexin 43 (Cx43) is essential for the transmission of electrical impulses between cardiomyocytes. Adequate expression of Cx43 is crucial for heart development, for the coordinated functioning of electrically coupled cardiomyocytes, and for the synchronization of myocardial function. However, many of the mechanisms involved are not yet fully understood and require further investigation (Zu *et al*., 2018). Thus, this study will highlight the findings in the literature on the diversity of gap union functions, emphasizing their relevance in the cardiovascular system and the potential role they play in various pathologies.

2) METHODOLOGY

The present study is a literature review of the narrative type. The search terms used were: "*Junction communication*", "*Gap Junction*", "*connexin* 43", "Cardiovascular System", through consultations to the databases of scientific articles Portal *Scopus* CAPES, *PubMed*, Scientific Electronic Library Online (SCIELO) and Google Scholar .Articles dating from 1952 to 2024 were searched.

3) RESULTS:

3.1) GAP JUNCTIONS:

Gap junctions are present in practically all types of vertebrate cells, with the exception of some cell types such as: erythrocytes, thrombocytes, mature skeletal muscle fibers and spermatozoa

(Willecke *et al*., 2002; CRUCIANI and MIKALSEN, 2002; Sáez *et al*, 2003; NIELSEN *et al*., 2012.; Figueroa and Duling, 2009; Wit and Peters, 2012).

Gap junctions have as their main characteristic that allow the cytoplasm of adjacent cells to exchange ions and small messengers. This exchange of information is necessary for the maintenance of the function of various tissues (Flagg-Newton *et al*., 1979; Hervé *et al*., 2004). This intercellular communication plays a key role in several physiological processes and consequently, any disruption in connexin function can lead to diseases (De Maio; Vega; Contreras, 2002; Yasarbas *et al* 2024).

These channels also play a role in autocrine and paracrine signaling, providing a pathway for the release of ATP (Dale, 2008), glutamate (Ye *et al*., 2003), NAD+ (Bruzzone et al., 2001) and prostaglandins (Cherian et al., 2005) and glucose (Neijssen *et al*., 2007; Bruzzone *et al*., 2001; Cherian *et al*., 2005). Thus, the connexins perform functions even if they are not forming the gap junction, so that the unconnected hemicanal performs the function of autocrine signaling (Moreno, 2004).

Hansson and Skiöldebrand (2015) presented several structures in the human body that have networks of cells coupled by gap junctions that express signaling systems for Cx43 and Ca^{2+}. The modifications of these signaling networks are associated with several pathologies in the body, highlighting their action on the cardiovascular system (Van Der Velden and Jongsma, 2002; Wang *et al*., 2016).

Important biological functions are attributed to these junctional channels, including cardiomyocyte beat synchronization (Rook *et al*., 1990). Given its essential functions, connexin expression and channel activity are strictly controlled by several factors, such as extracellular Ca^{2+} concentration, intracellular pH, membrane potential, post-translational modifications, and epigenetic regulation (Aasen *et al*., 2018; 2019; Yasarbas *et al*, 2024).

Connexin channels are sensitive to variations in the pH of the environment. When there is a reduction in pH, the closure of Cx43 channels occurs, a process mediated by conformational changes in the cytoplasmic domains, which act as gating plugs in response to acidic conditions (Peracchia, 2004).

These channels have the property of closing when the concentration of calcium increases and are responsible for chemical and electrical couplings between cells, such as in cardiac muscle tissue to allow the rapid transmission of electrical signals (Van Der Velden and Jongsma, 2002; Leithe; Mesnil and Aasen, 2018).

In addition to these direct effects, Ca^{2+} also regulates its transport by interacting with the Ca^{2+}-binding protein, calmodulin. Studies have shown that calmodulin binding results in Cx43 channel closure, suggesting that Ca^{2+}/calmodulin mechanisms are involved in channel activation (Xu *et al*., 2012).

3.2) CONNEXIN 43

Conexina 43, as well as all connexins, are divided into nine structural domains. There are four transmembrane domains with a α-helix structure; a C-terminal portion; an N-terminal portion;

two extracellular loops; an intracellular or cytoplasmic loop between transmembrane regions 2 and 3, characterized by representing the region of least similarity and least conservation among connexins (Kumar and Gilula, 1996; Hervé *et al*., 2004).

In the plasma membrane, the connexins are arranged in hexamer forming the junctional hemicanal, called connexon, this topological membrane organization is characteristic and similar for all subtypes of connexins (Makovski *et al*., 1977; Dermietzel and Spray, 1993; Kumar and Gilula, 1996; White *et al*., 1999; Unger *et al*., 1999; Segretain and Falk, 2004; Lily at al., 2015; Leithe; Mesnil and Aasen, 2018). These connections, once located in the membrane, can interact in a non-covalent way with the connexon of the adjacent cell, thus forming a complete junctional channel (Bennett *et al*., 1991).

The hemichannels formed by Cx43 are highly expressed in several cells, such as: cardiomyocytes, microglia, astrocytes and endothelium, and are highly sensitive to (Damage-Associated Molecular Patterns) DAMPs and (Pathogen-Associated Molecular Patterns) PAMPs (Moreno *et al*.2004; Contreras *et al*., 2004; Hansson and Skiöldebrand, 2015).

Considering that Cx43 hemichannels are tightly controlled under resting conditions, the presence of DAMPs and PAMPs can trigger pore opening. The channels become active under conditions of mechanical or ischemic stress and allow the release of molecules such as ATP, glutamate, and NAD+, eliciting different physiological responses (Lilly *et al*., 2015).

The carboxy-terminal domain of Cx43 plays a role in the trafficking, localization and turnover of channels through numerous post-translational modifications and protein interactions, binding to multiple proteins that can modulate the function of the channel, several techniques have been used to identify the interaction between these proteins throughout the connexin cycle (Sorgen *et al*., 2018).

In some cell types, Cx43 is expressed in abundance under basal conditions, such as cardiac myocytes (Rouach *et al*., 2002), smooth muscle or neurons (Severs *et al*., 2004). Cx43 participates in protection against cardiac injury, remodeling, differentiation, ion conduction, and regeneration (Michela, *et al*., 2015; Boengler and Schulz, 2017).

3.3) CONNEXIN 43 IN THE CARDIOVASCULAR SYSTEM

Silvio Weidman, in 1952, demonstrated that the electric current injected into a cell of the Purkinje fiber spread over a distance greater than the length of a single cell. This result suggested that the electrical charge could move rapidly between two cells through a low-resistance conduit (Weidman, 1952). Since then, the structure, composition and function of the channels of the gap junctions have been the subject of research.

The electrical coupling of cardiac muscle cells occurs through gap junctions that allow action potentials to be propagated in a uniform and orderly manner, including activities such as maintaining normal heart rhythm, regulating vascular tone, and endothelial function (Luke *et al*., 1989; Fromaget *et al*., 1992; Peracchia, 2004; Michela, *et al*., 2015; Boengler; Schulz, 2017), and their distribution are regulated during the embryonic stage.

In embryonic stages, the sites of expression of Cx43 are visible in the form of small dots, the abundance of which increases as development progresses. During these stages, immunoreactive sites are distributed in a relatively homogeneous pattern throughout the myocyte membrane. One week after birth, Cx43 expression is restricted to the ends of the myocytes, where the intercalated discs develop, as well as the adjacent lateral regions. This polarization of Cx43 becomes more pronounced until the third week after birth (Fromaget *et al*., 1992; Michela *et al*., 2015). In adulthood, ventricular connections formed by Cx43 predominate in the terminal intercalated discs, in addition to being present in some lateral regions of cardiomyocytes (Spray and Burt, 1990; Fromaget *et al*., 1992).

In addition to being located in the plasma membrane, Cx43 is also found in the mitochondria of cardiomyocytes, where it plays a crucial role in mitochondrial function by influencing oxygen consumption and potassium flows. Cx43 expression, both in the cell membrane and in the mitochondrial, is altered in several pathophysiological conditions, including hypertension, hypertrophy, hypercholesterolemia, ischemia/reperfusion injury, post-infarction remodeling, and heart failure (Michela, *et al*., 2015; Boengler and Schulz, 2017).

Cx43 in the heart is found both in ventricular myocytes in large quantities and in atrial myocytes and in the bundle of His and distal Purkinje fibers, and is located in the intercalated discs of the individual myocytes in both compartments of the heart, while Cx40 is expressed mainly in the atria and Purkinjee fibers, while Cx45 is found in low levels in ventricular myocytes, and it seems to co-locate with Cx43 in the intercalated disc (Davis *et al*., 1994; Beyer *et al*., 1995; Saffitz and Schuessler, 2000; Van Veen *et al*., 2001; Yamada *et al*, 2003; Meens; Kwak and Duffy, 2015).

In cardiac tissues, gap junctions play a fundamental role in the propagation of electrical impulses and the orientation of heart rhythm (Yeager, 1998; Moreno, 2004; Desplantez *et al*., 2007; Severs *et al.*, 2008).

This structure represents a pathway of low electrical resistance, facilitating the propagation of the electrical impulse and allowing the synchronism of cardiac contraction responsible for the pumping of blood (Weidmann, 1952; Desplantez *et al*., 2007), but it has other roles, being essential for cardiac remodeling after a heart attack (Schwanke *et al*., 2002).

The exact nature of myocyte-fibroblast coupling during remodeling in *vivo* and how fibroblasts influence electrical conduction in cardiac muscles is still debated (Kohl and Gourdie, 2014; Yokota *et al*., 2020). Recent optogenetic experiments have confirmed the existence of coupling of connections, forming gap junctions, between fibroblasts and cardiomyocytes (Wang *et al*., 2023).

However, studies suggest that fibroblast-myocyte coupling in scar tissue may be responsible for arrhythmogenesis, due to changes in the membrane potential of fibroblasts electrically coupled with myocytes (Wang *et al*., 2023; Sridhar and Clayton, 2024). Importantly, this potential occurs through gap junctions (Lillo et al., 2023) and these myocyte-fibroblast interactions have the potential to modify tissue electrophysiology and dynamics through conduction delays and the excitation of resting regions (Rog-Zielinska, 2016).

The diversity of expression of these proteins (Table 1) allows the assembly of heteromeric channels. The Cx43 is the most abundant connexin in the heart as compared to Cx40 and Cx45, which are expressed at lower levels in this organ (De Maio; Vega and Contreras, 2002; Kar *et al.*, 2012). The expression of Cx43 is modulated by different factors, which seem to act at the transcriptional level. Basic fibroblast growth factor (FGF) has been shown to stimulate *Cx43* expression in cardiac fibroblasts (Doble and Kardami, 1995).

Table 1 – Location of Connexins in the Cardiovascular System

Structure of the heart	Connexin	Reference	DOI
Atria	CX40	Beblo *et al*, 1995	10.1161/01.res.77.4.813
Atria	Cx40, Cx43	Yang *et al*., 2023	10.2147/DMSO. S419189
Atria	Cx43	ten Velde *et al.*, 1995	10.1161/01.res.76.5.802
Atria	Cx40, Cx43, Cx45	Verheule *et al.*, 1997	10.1161/01.res.80.5.673
Atria	Cx45	Zhang *et al*., 2020	10.1161/CIRCRESAHA.119.315539
Not but atrial	Cx45	Jansen, 2010	10.1016/j.yjmcc.2009.08.018
Ventricles	Cx43, Cx45	Rubart *et al.*, 2018	10.1093/cvr/cvx163
Ventricles	Cx40, Cx43, Cx45	Kanter *et al.*, 1994	10.1006/jmcc.1994.1103
Ventricular Natria	Cx45	Zhang *et al*., 2020	10.1161/CIRCRESAHA.119.315539
Ventricular Natria	Cx40, Cx43	Gourdie *et al*., 1993	10.1242/jcs.105.4.985
His Beam	Cx40	Gourdie *et al.*, 1993	10.1242/jcs.105.4.985
Purkinje Fibers	Cx40	Van Kempen *et al*., 1995	10.1002/jemt.1070310511
Purkinje Fibers	Cx40	Tracy *et al*, 2020	10.1007/s13239-020-00478-8
Purkinje Fibers	Cx40, Cx43	Gourdie *et al.*, 1993	10.1242/jcs.105.4.985
Cardiac endothelium	Cx37	Reed *et al*., 1993	10.1172/JCI116321
Cardiac endothelium	Cx40	Bastide *et al*, 1993	10.1161/01.res.73.6.1138
Cardiac endothelium	Cx37, Cx43	Lyons *et al*., 2021	10.1172/jci.insight.140952

The different combinations formed by connexins in the tissue are related to the modulation of cardiac tissue activities, leading to different electrical conduction properties and influencing

the synchronism of the beats (Moreno, 2004; Kar *et al.*, 2012). The flow of molecules through gap junctions is determined by the chemical and electrical gradient between two connected cells (Sáez *et al.*, 2003).

Cardiac connexins have the ability to form homotypic channels, composed of a single connexin isoform, as well as heterotypic channels, which consist of more than one connexin isoform (Moreno *et al.*, 2004; Desplantez *et al.*, 2007). This diversity creates a setting prone to complex patterns of conductance in the heart. In regions where an isoform is predominant, such as in the ventricular myocardium, where Cx43 is the main connexin, conductance is based on Cx43 activity.

However, in the atria, Cx40 is present, together with Cx43, and electrophysiological studies indicate that the interaction between Cx40 and Cx43 results in the formation of heterotypic rectifying gap junctions, which impacts electrical conduction in the atria (Beauchamp *et al.* 2006; Lin *et al.*, 2014; Meens, Kwak and Duffy, 2015).

Cx43-deficient mice die after birth as a result of ventricular arrhythmia (Reaume et al., 1995). Its role in the body's vasculature facilitates communication between the cells that make up the blood vessel wall and coordinates the regulation of vascular tone, so the coupling of vascular smooth muscle cells may be responsible for the synchronous contraction of small blood vessels (Willecke *et al.*, 2002).

Intracellular accumulation of Na^+ and loss of K^+ play important roles in the pathogenesis of arrhythmias and lesions in the ischemic heart. Kondo *et al.* (2000) show electrophysiologically that the removal of extracellular Ca^{2+} ions allows the activation of non-selective current that may play a role in altering ion flows, promoting arrhythmias and myocardial infarction.

3.4) CONNEXIN 43 ASSOCIATED PATHOLOGIES

Different articles presented structures in the human body that have networks of cells coupled by gap junctions that present a signaling system for Ca^{2+} including relating the modifications of these networks to pathologies in the body (Bruzzone and Ressot, 1997; Evans and Martin, 2002; Meşe and Richard, 2007; Hervé and Derangeon, 2013; Hansson and Skiöldebrand, 2015).

Mutations in connexin 43 can lead to the appearance of cardiac malformations that lead to decreased animal survival, as demonstrated in Knockout mice for Cx43 (Severs *et al.*, 2004).

Previous studies have shown that changes in cardiac development in fetuses with Cx43 deletion resulted in a delay in the development of the right atrium, leading to chamber dilation and malformations in the tricuspid valve, causing the death of the animal within a few hours (YA *et al.*, 1998; NIELSEN *et al.*, 2023).

In humans, carriers of Cx43 mutations have visceroatrial heterotaxy syndrome characterized by laterality and transposition of large arteries (Britz-Cunninghan *et al.*, 1995; Splitt *et al.*, 1995; Bruzzone *et al.*, 1996). In pathologies associated with the heart, it is known that during myocardial ischemia, Cx43 is dephosphorylated and the activity of several protein kinases and phosphatases is affected (Kondo *et al.*, 2000; Dale *et al.*, 2008). The first few minutes of

ischemia do not affect the partially phosphorylated state of Cx43, but prolonged ischemia corresponds to dephosphorylation of Cx43 (Dale *et al.*, 2008).

Data from Green and Severs (1993) demonstrated alterations in the distribution of Cx43 protein in the hearts of patients who developed ischemic heart disease after myocardial infarction.

Remodeling of connexin expression and gap junctions has been documented in several heart diseases (Table 2), particularly in ischemic conditions and heart failure. This remodeling can be manifested both by changes in the distribution of gap junctions and by variations in the amount and type of expressed connexins.

Changes in Cx43 and disorders in gap junctions are associated with ventricular diseases, arrhythmogenic changes, and contractile dysfunction. In addition to ventricular changes, these histological changes have also been linked to the onset and persistence of atrial fibrillation, the most common form of atrial arrhythmia, although these findings are not yet fully clarified (Severs *et al.*, 2008). Heart rhythm abnormalities are a common, serious, and often fatal complication of many forms of heart disease.

Table 2 – Connexin 43 in the Cardiovascular Diseases

Cardiovascular pathology	Connexin	Expression	Reference	DOI
Atrial fibrillation	Cx43	-	Bikou *et al.*, 2011	10.1093/cvr/cvr209
Aterosclerose	Cx43	+	Kwak, 2002	10.1161/hq0102.104125
Chronic myocardial infarction	Cx43	-	Peters, 1995	10.1002/jemt.1070310507
Fibrose atrial	Cx43	-	Lousinha, *et al.*, 2020	10.1016/j.yexmp.2020.104409
Heart failure	Cx43	-	Kostin, 2007	10.1111/j.1582-4934.2007.00063.x

4) DISCUSSION:

Gap junctions are transmembrane channels that play an important role in intercellular communication in various cell types and different tissues (Fortes *et al.*, 2004; Zeitz and Smyth, 2023), acts in the propagation of injury signals by enabling the exchange of ions and substances such as amino acids, nucleotides, ATP, cAMP, glucose, $Na^{+,}$ and second messengers, which can be observed in the propagation of Ca^{2+} waves dependent on inositol triphosphate (IP3) and other metabolites and ions in a wide range of pathologies (Bennett *et al.*, 1991; Dhein, 1998; Giepmans, 2004; Neijssen *et al.*, 2007).

The formation of gap junctions is susceptible to the influence of specific mutations that can result in connexins having a defective intracellular location, therefore interfering with the transport and insertion of the hemichannel into the cell membrane (Himelman, *et al*, 2020, Zong *et al.*, 2023).

It is well established that Cx43 has multiple phosphospecific residues, which can be regulated by several kinases (Lampe and Lau, 2004; Lampe *et al*., 2006; Kadle, Zhang and Nicholson, 1991; Lau, Hatch-Pigott and Crow, 1991). Some phosphorylation events act to close the gap junction channel (Morel and Kwak, 2012; Arellano, Rivera, and Ramon, 1990), while others seem to keep the channel in the open configuration (Lampe and Lau, 2004). In addition, connexins, like phosphoproteins, are also regulated by dephosphorylation, and the protein phosphatase-1 has been shown to interact with Cx43 to modulate its phosphorylation state (Duthe *et al*., 2001; Kang *et al.*, 2014; Meens; Kwak and Duffy, 2015).

The study by Himelman *et al.* (2020), showed that in the hereditary neuromuscular disease, X-linked Duchenne muscular dystrophy (DMD), Connexin 43 has its phosphorylation reduced, thus inferring that this could be a key mechanism in the remodeling of Cx43 in pathologies that affect the cardiovascular system.

The direction of Cx43 to intercalated discs was also affected due to the interruption of the membrane connection machinery when cardiomyocytes are subjected to oxidative stress (Nielsen *et al*, 2023). The transport and positioning of Cx43 is a mechanism dependent on microtubules and actin (Basheer and Shaw, 2016). Associated with this, there is the possible attributions of Cx43 in the regulation of the cell barrier function. Indicating that connexins influence cytoskeletal dynamics and cell-cell contact arrangements (Zhang *et al*., 2014).

Therefore, the cytoskeleton with the actin filaments intact seems to be a prerequisite for the localization and function of Cx43, thus raising the hypothesis that actin filaments may be necessary to stabilize junctional canal coupling during periods of intense mechanical loading and cellular stress (Basheer and Shaw, 2016).

Junctional channels are associated with several proteins that could act by modulating the functioning of the channel. It has been shown that Cx43 associates with the cytoskeleton through direct interactions between the C-Terminal portion of connexin and several binding proteins such as actin, ZO1, α- and β-tubulin (Sorgen *et al,* 2018). A protein that has been highlighted in several studies is ZO-1 (Ambrosi *et al.*, 2016; Zong *et al*., 2023).

The distributions of ZO-1 and connexin 43 were studied in samples from healthy patients with heart failure, using the immunohistochemical technique of double labeling and confocal microscopy, where it was possible to observe that ZO-1 was colocated with connexin 43 in intercalated discs (Kostin, 2007; Meens, Kwak and Duffy, 2015).

It is important to note that, in patients with heart failure due to dilated or ischemic cardiomyopathy, regions where Cx43 expression was decreased were also characterized by reduced ZO-1 labeling. Based on these data, it is understood that in patients with heart failure, ZO-1 downregulation corresponds to decreased expression levels of connexin 43, suggesting that ZO-1 plays an important role in gap junction formation and junctional plaque stability (Kostin, 2007).

The channels responsible for the electrical coupling of cardiomyocytes are composed of proteins encoded by the connexin family of genes (Willecke *et al* 2002; Michela *et al*,

2015). As previously discussed, the various types of connexin expressed in the heart (Cx43, Cx40 and Cx45) are found in different combinations and different amounts (Severs *et al*, 2008).

A relevant feature of acquired structural heart disease is the remodeling of the expression and localization of the concomitant connexin protein with increased susceptibility to lethal arrhythmias, suggesting that the two are associated (Gutstein *et al*, 2001; Hesketh *et al*, 2009).

Increased expression of Cx43 improves cardiac dysfunction, however, Cx43 is decreased in patients with Arrhythmogenic Cardiomyopathy (Coscarella *et al*., 2022).

The presence of Cx43 in mitochondria is widely recognized, with several studies indicating that the amount of Cx43 in mitochondria increases in response to ischemia-reperfusion (Rodriguez-Sinovas *et al*., 2006) and that this protein plays a role in regulating cellular apoptosis (Goubaeva *et al*., 2007).

Mitochondrial Cx43 regulates potassium levels in the matrix and plays a role in the heart's energy metabolism (Sepp; Severs and Gourdie, 1996; Schultz *et al*., 2016). The influx of K^+ through mitoK^+ATP channels causes mitochondrial depolarization in preconditioned cardiomyocytes. This phenomenon is related to the reduction in the production of reactive oxygen species and the decrease in the size of the infarction, and is essential for cardioprotection (Yue *et al*., 2002; Michela *et al*., 2015).

Based on this, we can infer that both diseases of genetic origins and acquired pathologies can lead to changes in connexin levels. To the extent that changes in the expression and positioning of connexin can trigger the worsening of pathologies. As a result, connexins become a relevant avenue for studies of possible treatments for various diseases.

5) CONCLUSION

In this article, we examine the functional and structural abnormalities of Cx43 in heart disease, highlighting lateralization of Cx43 as a common event in all cardiovascular diseases, which often present with abnormal rhythms and conduction. In addition, we discuss the role of connexin in mitochondria. The increasing attention to changes in Cx43 suggests significant therapeutic potential, offering new perspectives for clinical interventions in cardiac pathologies.

In this way, we highlight that the gap junctions formed by different connexins constitute the crucial intercellular pathway for the transmission of the cardiac impulse. The specific expressions and functions of connexins reflect the pathophysiological changes associated with various conditions.

6) RECOMMENDATIONS

The study of connexins opens up several possibilities for understanding cardiac diseases of genetic origin as well as acquired pathologies. In this context, connexins emerge as promising targets for the development of therapeutic strategies, offering new perspectives for the treatment of a wide range of cardiac diseases.

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