GAP JUNCTION: Emphasis on Connexin 43

JUNÇÃO COMUNICANTE: Ênfase na Conexina 43

Gabriella Oliveira Alves Moreira de Carvalho [1,2], Olga Maria de Jesus Souza[2,3], Fabio da Silva de Azevedo Fortes[2,3]

AUTHOR AFILIATIONS

1– Precision Medicine Research Center (CPMP); Institute of Biophysics Carlos Chagas Filho; Federal University of Rio de Janeiro – UFRJ
2 – Laboratory of Cellular and Molecular Therapy and Physiology Prof. Antônio Carlos Campos de Carvalho (LTFCM)
3 – Program in Translational Biomedicine (BIOTRANS) - UERJ, UNIGRANRIO, Inmetro, Rio de Janeiro

ORCIDS AND CONTACT

Gabriella Oliveira Alves Moreira de Carvalho
Orcid: 0000-0001-6198-7054
gabriellacarvalho_15@yahoo.com.br
Olga Maria de Jesus Souza
Orcid: 0009-0002-6180-5227
olgasouza23@yahoo.com.br
Fabio da Silva de Azevedo Fortes
Orcid: 0000-0003-2385-6023
fabiofortes.uerj@gmail.com

ABSTRACT

The junctions of the cell are complex structures that play a fundamental role in cellular communication. They are morphologically distinct and are divided into occlusion junctions, adherens junctions and gap junctions. This review has the objective of providing the main information about the gap junctions demonstrating its components and highlighting their role in cellular maintenance, emphasizing the studies of junctions, formed by connexin 43 (Cx43), which is widely found in various tissues, highlighting its function in the main systems, the formation cycle and possible interactions. For this, we searched the databases: CAPES, Scielo, Scopus, Science Direct and PubMed using keywords and selecting the articles with the inclusion and exclusion criteria to structure a document for students and researchers of the areas of cellular biology, biophysics and physiology.

Keywords: Gap junction, Connexin 43, GJA1.

RESUMO

As junções celulares são estruturas complexas que desempenham um papel fundamental na comunicação celular. Elas são morfologicamente distintas sendo divididas em junções de oclusão, junções aderentes e junções comunicantes (*gap junctions*). Este trabalho revisional tem como o objetivo fornecer as principais informações sobre as Junções comunicantes demonstrando seus componentes e destacando seu papel na manutenção celular, enfatizando os estudos das *junções*, formadas pela conexina 43 (Cx43), que é vastamente encontrada em diversos tecidos, destacando sua função nos principais sistemas, o ciclo de formação e as possíveis interações. Para isso, foi realizado uma busca nas bases de dados do portal de periódicos da CAPES, *Scielo*, *Scopus*, *Science Direct* e *PubMed* utilizando palavras-chaves e selecionando os artigos com os critérios de inclusão e exclusão para estruturar um trabalho destinado a estudantes e pesquisadores das áreas de biologia celular, biofísica e fisiologia.

Palavras-chave: Junção comunicante, Conexina 43, GJA1.

INTRODUCTION

Among the various forms of intercellular communication, the one that allows direct communication between tissue cells stands out, and this occurs through the communicating junction or “gap junction”, characterized by transmembrane channels that enable direct communication in tissues (Dhein, 1998).

From the end of the 1950s, several works

helped to characterize such structures. The first detection of gap junctions was obtained from electrophysiological experiments in crayfish neuronal cells (Furshpan & Potter, 1959) and, later, other experiments using more advanced analysis techniques, demonstrated their structure and allowed the characterization of this communication pathway (Neijssen et al., 2007). In view of this, the present study aims to review in the literature the knowledge acquired about the main functions of gap junctions in the body's physiology, highlighting the roles associated with connexin 43. In addition to describing gap junctions, highlighting their structure, formation and importance in cell maintenance.

METHODOLOGY

The search terms used were: "Junction comunication", "Gap Junction", "connexin 43", "GJA1", through consultations with the databases of scientific articles Portal Scopus CAPES and PubMed. Articles dating from 1959 to 2018 were searched. A qualitative approach of the descriptive type of the theme involving gap junctions mediated by connexin 43 was carried out.

LITERATURE REVIEW

Gap Junctions

The beginning of the description of gap junctions occurred at the end of the 50s by Furshpan & Potter (1959). These researchers presented the first evidence of intercellular communication with data that showed electrical coupling in crayfish neurons. Other works have demonstrated electrical coupling in other cell types, but without stating that the gap junction would be responsible for this phenomenon.

In the late 1960, transmission electron microscopy experiments on samples previously treated with lanthanum nitrate allowed the visualization of heptalaminar structures, presenting a hexagonal pattern of subunits 7 to 8 nm in diameter, and with spaces of approximately 2 nm between the membranes of adjacent cells (Revel & Karnovsky, 1967).

In 1970 Uehara and Burnstock presented a transmission electron microscopy image with a structure that the authors described as “precise and located at the closest approximation of the membranes of smooth muscle cells”, being similar to a fusion between the membranes, but in fact they were of a “Gap” junction.

Using X-ray diffraction techniques, the junctional structure was better elucidated. (Makovski et al., 1977). The observations demonstrated that the channel was formed by six monomers that form a pore with a diameter of 1.5 nm, allowing communication between the membranes of adjacent cells to occur through the alignment of the hemichannels on the membrane. (Laird, 2006; Goodenough & Paul, 2009; Koval et al., 2014; Laird, 2014).

The aligned hemichannels acquire a tubular format reaching a total length of 100 – 150 Â, being in the cell membranes at a distance of approximately 20 Â (Dhein, 1998). After the morphological findings, the correlation of junctions with electrical coupling became more evident. (Gilula et al., 1972).

Thus, gap junctions are hermetically closed transmembrane channels located in the extracellular cleft (Giepmans, 2004), which play an important role in intercellular communication in different cell types and in different tissues (FORTES et al., 2004), as they allow communication bidirectional (Bermudez-Fajardo et al., 2007), direct from the cytoplasm of two neighboring cells. In addition to being a low-resistance pathway for the propagation of electrical impulses in mammals, the junctional channel allows the movement of molecules of up to 1 kDa (Flagg-Newton et al., 1979; Koval et al., 2014), enabling the exchange of ions and substances such as amino acids, nucleotides, ATP, cAMP and second messengers, which can be observed in the propagation of Ca^{2+} waves dependent on inositol triphosphate (IP3) (Bennett et al., 1991; Dhein, 1998; Giepmans, 2004; Neijssen et al., 2007).

Structure of Gap Junctions

Connexins are divided into nine structural domains. There are four transmembrane domains with an α-helix structure (TM1, TM2, TM3 and TM4); a C-terminal portion; an N-terminal portion; two extracellular loops (E1 and E2); an intracellular or cytoplasmic loop between transmembrane regions 2 and 3, characterized by representing the region of least similarity and least conservation between connexins (AC) (Kumar & Gilula, 1996; Herve et al., 2004).

The transmembrane domains and the extracellular loops are the regions that show the greatest phylogenetic conservation among members of the connexin family, while the carboxy-terminal domain and the others show little phylogenetic conservation (Bennett et al., 1991; Dhein, 1998). As the most amphipathic region, transmembrane domain 3 constitutes the central region of the junctional canal, forming the walls of the canal (Unger, 1999).

The connexins can be differentiated by the molecular weight parameters, in kDa that varies between 25 and 62 kDa, coming from the

complementary DNA sequences (cDNA), so connexin 43 has 43 kDa (Neijssen et al., 2007).

With this, the connexins are divided into two phylogenetic branches: Group I, formed by connexins with a molecular weight lower than 32 kDa; Group II, consisting of connexins with molecular weight equal to or greater than 32 kDa (Bennett et al., 1995; Dhein, 1998; Sosinsky & Nicholson, 2005).

These proteins are also classified into α and β subgroups according to the similarity between certain regions of the connexin primary protein sequence (Gimlich et al., 1990; Willecke et al., 2002; Segretain & Falk, 2004), thus their nomenclature can still be encoded by the family of genes related to its synthesis from the mapping of four functional genes (α 1 , β 1 , β 2 e α 3) So the respective names for connexin 43, connexin 32 and connexin 46 are GJA1, GJB1 and GJA3 (Hsieh et al., 1991; Kumar & Gilula, 1996; Meşe et al., 2007).

So far, 21 types of connexins have been reported in humans and 20 types of connexins in rodents (Sohl & Willecke, 2004; Herve, 2005; Sánchez et al., 2019). In humans the gene is located on the chromosome 6q22-q23 (Paznekas et al., 2003).

In the plasma membrane, the connexins are arranged in hexamer forming the junctional hemichannel, called conexon, this topological organization of the membrane is characteristic and similar for all subtypes of connexins (Makovski et al., 1977; Dermietzel & Spray, 1993; Kumar & Gilula, 1996; White et al., 1999; Unger et al., 1999; Segretain & Falk, 2004; Lily at al., 2016). These connexons, once located in the membrane, can non-covalently interact with the connexon of the adjacent cell, thus forming a complete junctional channel. (Bennett et al., 1991).

With this, twelve connexins interact with each other to form a junctional channel, six connexins are organized in a hexamer in the plasmatic membrane of a cell, once parallel with the adjacent cell the conexon can align and another conexon and form the junctional channel (Koval et al., 2014). This channel only becomes functional when turned on, allowing the passage of substances of up to 1 kDa (Fortes et al., 2004).

The connexon can be classified according to its composition: when made up of the same connexins, for example, all formed by connexin 43 (Cx43), they are called homomeric connexons, and when their composition has different connexins they are called heteromeric connexons (Wang & Peracchia, 1998; Lily et al., 2016).

The hemichannel is also classified according to its composition, this takes into account the relation to the complete junctional channel, and can be classified as: homotypic and heterotypic, respectively, when the connexins of the paired connexons belong to the same family

or different families. (Meşe et al., 2007; Koval et al., 2014).

Therefore, the entire structure of the hemichannel can be classified according to its composition, as follows: (1) homomeric – homotypic, the channel consists of two identical connexons formed by the same connexin; (2) homomeric– heterotypic, the channel is formed by two different connexons, each connexon being formed by the same connexin; (3) heteromeric – homotypic, the channel is formed by two identical connexons that are constituted by different connexins, with the connexins of one connexon aligned with connexins of the same type in the other connexon; (4) heteromeric – heterotypic or biheteromeric, where the channel is formed by two different connexons constituted by different connexins, and these aligned with connexins different from the other connexon (Kumar & Gilula, 1996; Meşe et al., 2007); (5) monoheteromeric, where only one of the connexons is heteromeric (Sosinsky, 1999; Koval et al., 2014).

Hetero-oligomerization is a regulated process that acts directly on the regulation of the role played by hemichannels in human physiology by changing the affinity for different substances (Koval et al., 2014), but not all combinations of isoforms are compatible.

Formation of Gap junctions

Connexins are synthesized by ribosomes in the endoplasmic reticulum, being fully co-translated in the rough endoplasmic reticulum membrane (Loewenstein, 1981; Segretain & Falk, 2004; Laird, 2006; Lily at al., 2016). Still in the rough endoplasmic reticulum, the connexin is phosphorylated and can be oligomerized and transported to the Golgi complex. (Falk, 2004; Koval et al., 2014). After oligomerization, the connexin forms the hexamer, called a conexon (within exocytic vesicles) which is transported from the Golgi complex to the plasmatic membrane of the cell, through microtubules (Musil & Goodenough, 1993; Dhein, 1998, Gaietta et al., 2002; Segretain & Falk, 2004; Laird 2006).

Through assays with the recombinant protein Cx43, using confocal microscopy and transmission electronic microscopy techniques, Gaietta et al. (2002) observed that the preformed proteins are inserted in the borders of the gap junction plates located in the plasmatic membrane. As the plaque is repopulated with new connexins, the old connexins centralize until they leave the plaque within endocytic vesicles.

Throughout this process, it is believed that the integrity of the connexin and the oligomerized state of the connexon is maintained by non-covalent bonds, suggesting the existence of intramolecular and non-intermolecular disulfide bridges. (John & Revel, 1991; Laird, 2006).

In contrast to most junctional complex proteins, Cx43 is stabilized as monomers in the endoplasmic reticulum and only oligomerizes after transport to the Golgi apparatus. Part of this pathway is regulated by the control protein, ERp29, which binds to the second extracellular domain and stabilizes a conformation that favors monomeric Cx43 (Koval et al., 2014).

The time for the junction to start forming varies from 3 to 30 minutes, with a formation rate of 1.3 channels per minute (Dhein, 1998; Laird, 2006). The junctional channel is formed through the interaction of extracellular loops E1 and E2, this process being facilitated by adhesion proteins, such as cadherins, as these keep cells in contact (Musil & Goodenough, 1993). After the time the connexin remains in the plasma membrane, the dodecamer is internalized and eliminated by pathways involving endocytic vesicles, which will fuse with lysosomes and proteasomes (Yeager et al., 1998; Gaietta et al., 2002; Segretain & Falk, 2004). Since the half-life of Cx43 is approximately 1-2 h after its synthesis (Laird et al, 1991; Severs et al, 2006; Laird 2006).

Properties of Gap Junctions

The junctional channels alternate between states: open and closed (Unwin & Zampighi, 1980; Koval et al., 2014). In order to understand the opening and closing phenomena of the channel, electrophysiology techniques began to be used, more precisely patch clamp tests, making use of the double whole cell configuration, where pairs of cells are analyzed (White et al., 1985).

As described in Dhein's protocol (1998), to carry out the experiment, one of the cells has its membrane potential maintained at a fixed value called the holding potential, which can be at -40 mV, for example, while the other cell of the pair has its potential modified throughout the experiment, varying from -90 mV a +10 mV.

By varying the voltage of one of the cells, the current flow from the modified voltage cell to the fixed voltage cell is measured through the patch clamp amplifier, which injects enough current so that there is no voltage variation in the cell that has its potential kept fixed. This measured current is equal and opposite to that flowing through gap junctions, called the junctional current. (Dhein, 1998).

Several factors can influence the conductance of gap junctions. One of these factors would be the transjunctional voltage dependence, where variations may be responsible for opening or closing the channel. In homotypic channels this voltage dependence is symmetrical, with the junctional conductance being modified when changing the voltage in either of the two cells being analyzed (Bennett et al., 1991). In heterotypic channels, however, the change in junctional conductance depends on which of the two cells of the analyzed pair will have the voltage changed. (Werner et al., 1989).

The voltage dependence of gap junctions varies according to the connexin that forms the junctional channel. For example, connexins 40 and 45 are more sensitive to transjunctional voltage changes than other connexins such as Cx43 (Jongsma et al., 1993; Dhein, 1998). In addition to biophysical factors, several biochemical factors can modulate junctional conductance, depending on which connexin or tissue they are acting on.

The pathways related to protein kinase C (PKC), protein kinase A (PKA), protein kinase G (PKG), MAP-kinase and tyrosine kinases are related to the regulation of gap junctions (Dhein, 1998). Highlighting the PKA pathway, many studies have observed that stimulation of this pathway can increase the coupling of gap junctions formed by connexin 43 in cardiomyocytes (Burt & Spray, 1988).

Other factors may influence the conductance of gap junctions in addition to those already mentioned, such as some ions: Ca^{2+}, Mg^{2+} and H^{+}. High concentrations of Ca^{2+} in cardiomyocytes lead to a decrease in cell electrical coupling (Loewenstein, 1966), but if the intracellular pH is kept constant, this response does not occur, suggesting a synergistic action between H^{+} and Ca^{2+} (Noma & Tsuboi, 1987). The increase in intracellular concentrations of Mg^{2+} also leads to cell uncoupling, but in concentrations greater than physiologically tolerable levels (Noma & Tsuboi, 1987; Peracchia, 2004).

Another important factor, described in the regulation of gap junctions, is pH, which interferes by reducing conductance through intracellular acidification. By performing electrophysiology techniques, analyzing channels formed by Cx43, Delmar et al. (2000) demonstrated that the interaction of the carboxy-terminal portion with a separate region of the connexin is responsible for the sensitivity of the junctional channel to a decrease in cellular pH.

RESULTS

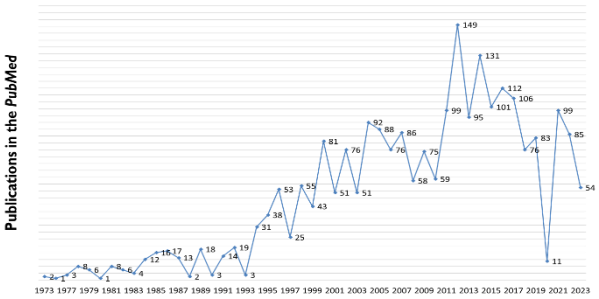

Figure 1: Revisional publications with the keyword "Junction Comunication". Quantitative survey of the number of publications per year in the PubMed database using the keyword “Junction communication”, searched on october 18, 2023 at five thirty-two minutes. Research 08/18/2023. Total: 2395.

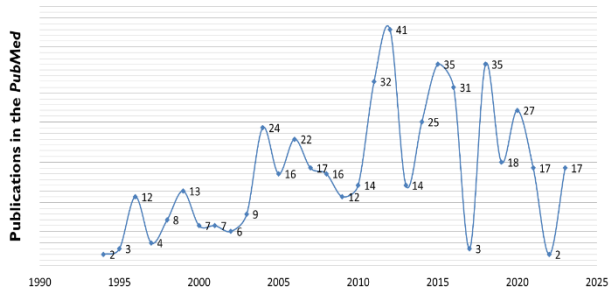

Figure 1: Revisional publications with the keyword chave "*Connexin* 43". Quantitative survey of the number of publications, per year, in the *PubMed* database with the search for the keyword “Connexin 43”, searched on october 18, 2023 at five thirty-three minutes. Research 08/18/2023. Total: 489.

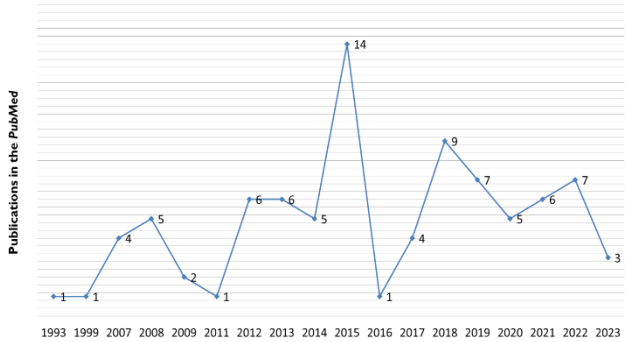

Figura 2: Revisional publications with the keyword chave "GJA1". Quantitative survey of the number of publications, per year, in the *PubMed* database using the keyword “GJA1”, searched on october 18, 2023 at five thirty-four minutes past five. Research 08/18/2023. Total: 87.

DISCUSSION

In the process of researching academic articles with the keyword “Junction communication”, it was verified that the beginning of the publication of articles related to the communicating junction began in the 70, the same decade of the advent of the Western Blotting technique, in 1973 with the first report of intercellular binding, but advances in research have been growing over the last 26 years. The increase in the number of publications occurred in 1993, with seasonal reductions that can be attributed to the restricted number of researchers working in this line of research.

The understanding of these structures and their role in the body also accompany the number of publications due to the advancement of technology, mainly the advancement of techniques used for microscopic and genetic analysis, thus emerging new research groups for this area.

The first article found with the keyword “Connexin 43”, searched in the PubMed database, was published in 1993, the same year that there was an increase in the number of publications on gap junctions.

The important role of this structure in the organism and its function in different systems influenced the first peak of publications on this topic in 1996, just three years after the identification of this structure. This fact may be related to the large distribution of Cx43 in the systems, leading to its identification with the advancement of scientific research techniques.

In the same decade of the Human Genome Project, a project that helped to understand physiological molecular arrangements and diseases, we found the first publication with the keyword “GJA1” in the PubMed database, despite the decrease in the number of publications from 2016. It is more common to use the nomenclature “Conexin 43” to refer to this structure and use it as a keyword, although many articles still cite “GJA1” in the body of the text.

Although some structures and functions are well described in the literature, there are still gaps in knowledge about gap junctions and about connexin 43 in different systems, making it important to continue existing lines of research and the emergence of new groups interested in elucidating this topic**.**

CONCLUSION

It is concluded that the study regarding the Communicating Junctions has advanced over the years and follows the advance of research techniques and analysis, highlighting the physiological role of these structures. More studies are needed to clarify the involvement of these structures in physiology and pathologies, providing information for potential therapeutic measures in the future.

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