Structure function relationship of gap junctions, the structure that permits heart cells to contract synchronously

The heart is constituted by cells that contract synchronously thereby allowing pumping of the blood to all the organs around the body of animals that possess a circulatory system. The trigger that initiates this contraction is an electrical current that is transmitted from cell to cell by structures called gap junctions that links the interior of the cells. This process is called electrical coupling and occurs about 70 times per minute in the human heart.

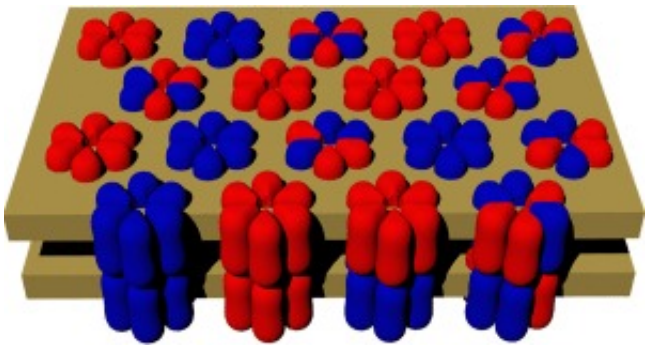

Fig. 1. Schematic representation of a gap junction in the case of the co-expression of 2 connexins (blue and red; the 2 brown plates represent the membrane of 2 electrically coupled cells, the narrow space in between is the extracellular space). Several arrangements of the connexins and connexons are represented which we know are not all possible with the connexins described in the summary and in the paper published in the J Mol Cell Cardiol (Desplantez et al, JMCC 2015 - 89:195-202).

These junctions are constituted by tightly packed channels permeable to ions that conduct these electrical impulses. Gap junctions are constituted by protein called connexins which are a family of related molecules composed of 21 members in mammals of which up to 3 are present in different regions of the human heart, connexin40 (Cx40), Cx43 and Cx45. Connected cells each provide 1 half channel called connexon constituted by 6 connexin molecules that bind outside the cells in the extracellular space. A complete gap junction channel is therefore made of 12 connexins. Channels made of a single connexin have specific electrical properties and regulation but since some regions of the heart have up to 3 connexins, a large number of channel compositions are plausibly present. If two connexins can freely assemble, 12 heteromeric (composed of variable number of connexins) and 2 homomeric (made of a single connexin) connexons may form. Furthermore, connexons made of different connexins can form channels called heterotypes and potentially 196 types of intercellular channels could be formed (see figure for examples of different possible theoretical channels).

In the diseased human heart and animal models of heart disease, alterations of connexins quantities is recognized as a major contributor to rhythm disorder that may lead to sudden cardiac death. For example, in the failing heart Cx43 is heterogeneously reduced whereas Cx45 is increased. Similarly, in atrial fibrillation, alterations of Cx43 and Cx40 amounts have been reported.

To gain more insight into the structural and functional consequences of different connexins quantity ratios, we have genetically engineered a cell line that naturally have Cx43 to produce Cx45 or Cx40 at variable, controlled levels, a process called induction. With this system different accurate ratios of Cx45:Cx43 and Cx40:Cx43 are obtained and structural studies (presence of heteromers and heterotypes) and functional studies (electrical coupling) have been performed.

When present at similar levels Cx43 and Cx40, heteromeric connexons are formed in low quantities (~12%) in Cx43+Cx40 cells but in Cx45+Cx43 cells we could not detect heteromers. Cx40, even in the presence of Cx43, does not form channels or at undetectable levels with cells that have Cx43 only while Cx43 channels are abundantly present. However, Cx45 form channels with Cx43 (heterotypic channels) and this configuration seemed favoured.

Distinct electrical coupling were observed: induction of Cx45 in Cx43+Cx45 cells leads to a lower electrical coupling than non-induced cells (with only Cx43), similar at all Cx45:Cx43 ratios, whereas the electrical coupling in cells containing Cx43 and Cx40 depends on the amounts of Cx40 with low levels inhibiting electrical coupling and high levels increasing it.

Altogether our data suggest distinct gap junctional channels make-up and function depending of the type and the ratio of connexins present in the cells. This study provides useful insights in understanding the contribution of cardiac connexins in regulating electrical impulse propagation brought by changes of connexins sub-types levels between cardiac regions that express different connexins.

***Desplantez Thomas*[1] *and Dupont Emmanuel*[2]**
[1]*IHU LIRYC, Université de Bordeaux, Inserm U1045, PTIB, Pessac, France*
[2]*Imperial College, Hammersmith Campus, London, UK*

Publication

Relating specific connexin co-expression ratio to connexon composition and gap junction function.
Desplantez T, Grikscheit K, Thomas NM, Peters NS, Severs NJ, Dupont E.
J Mol Cell Cardiol. 2015 Dec