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Cell-cell communication in diabetic retinopathy

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ABSTRACT

In diabetic retinopathy, high glucose (HG)-mediated breakdown in cell-cell communication promotes disruption of retinal homeostasis. Several studies indicate that HG condition alters expression of connexin genes and subsequent gap junction intercellular communication (GJIC) in retinal vascular cells and non-vascular cells. A serious consequence of disrupted cell-cell communication is apoptosis and breakdown of the blood-retinal barrier (BRB). More recently, studies suggest adverse effects from HG on retinal Müller cells. This article focuses on HG-mediated changes in connexin expression and GJIC and their subsequent effects on the breakdown of retinal homeostasis, cell death, compromised vascular permeability, and interactions between endothelial cells, pericytes and retinal Müller cells in the pathogenesis of diabetic retinopathy. Additionally, options for rectifying disrupted homeostasis under HG condition associated with diabetic retinopathy are reviewed.

1. Introduction

1.1. Connexins and gap junction intercellular communication in diabetic retinopathy

Gap junction intercellular communication (GJIC) is mediated by docking of connexin hemichannels on two adjacent cells to form conduits that allow communication of electrical signals between cells and the exchange of molecules that are less than 1 kD (Nielsen et al., 2012; Wright, Richards, & Becker, 2012). GJIC plays a vital role in maintaining tissue homeostasis and regulating cell survival (Dagli & Hernandez-Blazquez, 2007; De Maio, Vega, & Contreras, 2002; Li, Mruk, & Cheng, 2012; Wei, Xu, & Lo, 2004). Currently, twenty-one connexin isoforms have been identified in the human genome (Nielsen et al., 2012), which are characterized on the basis of their molecular weights (Nielsen et al., 2012). These connexins can form homomeric, homotypic, heteromeric and heterotypic gap junctions depending on the type and composition of the connexon subunits involved. Studies have identified different types of connexins that interact with each other in the eye (Vaney & Weiler, 2000). It is also well-known that cell death is a characteristic retinal lesion in early stages of diabetic retinopathy (Chistiakov, 2011). Studies report that connexin-mediated GJIC activities contribute to cell survival by allowing cells to exchange ions, metabolites, secondary messengers, energy molecules, glucose, ATP, and other free radical scavengers though gap junctions (Decrock et al., 2009). These findings underscore the importance of cell-cell coupling in regulation of cell growth, differentiation, development (Kojima et al., 2008; Wei et al., 2004) and cell survival (Plotkin, Manolagas, & Bellido, 2002). Importantly, connexin expression and subsequent GJIC activity are downregulated by HG condition contributing to retinal vascular cell loss and other retinal lesions associated with diabetic retinopathy (Fernandes, Girao, & Pereira, 2004; Li & Roy, 2009; Li, Sato, Haimovici, Okamoto, & Roy, 2003; Sato, Haimovici, Kao, Li, & Roy, 2002). Taken together, connexins play an integral role in maintaining homeostasis of the retinal microenvironment. Therefore, defining this exact role in the context of diabetic retinopathy is of significant importance.

2. Connexin structure

The connexin polypeptides oligomerize into a six-subunit structure known as a connexon (Cottrell & Burt, 2005). These connexons span from the cellular cytoplasmic space through the plasma membrane and out to the extracellular space. The two extracellular loops in Cx43 contain three cysteines, which are required for the docking of two hemichannels (Stains & Civitelli, 2005). The resultant structure created by the two docked hemichannels is a gap junction (Cottrell & Burt, 2005; Stains & Civitelli, 2005), which can be of four types, homomeric, heteromeric, homotypic or heterotypic as described in the next section. Schemes outlining the structure, cellular location, and docking of connexin channels are presented in Figs. 1 and 2.

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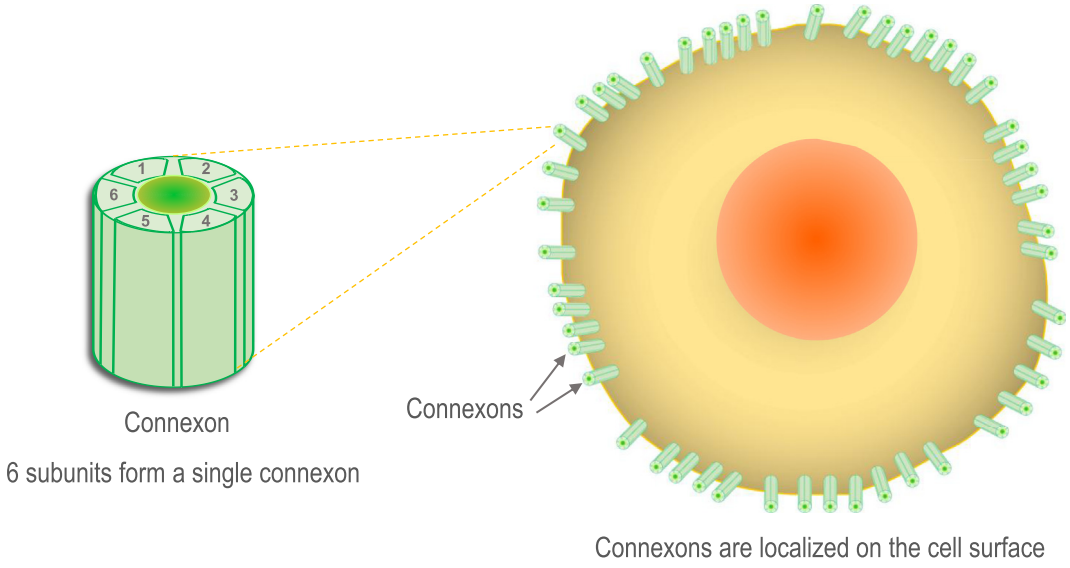

Fig. 1. Structure and localization of connexons. Each connexon is a hexameric channel comprised of six homomeric or heteromeric subunits. Connexons are localized on the cell surface; each connexon exhibits a cytoplasmic domain, a transmembrane domain, and an extracellular domain. The extracellular domain from two connexons play a critical role in docking and represent the "gap" junction or the space between the two cells where connexons form a connexin channel.

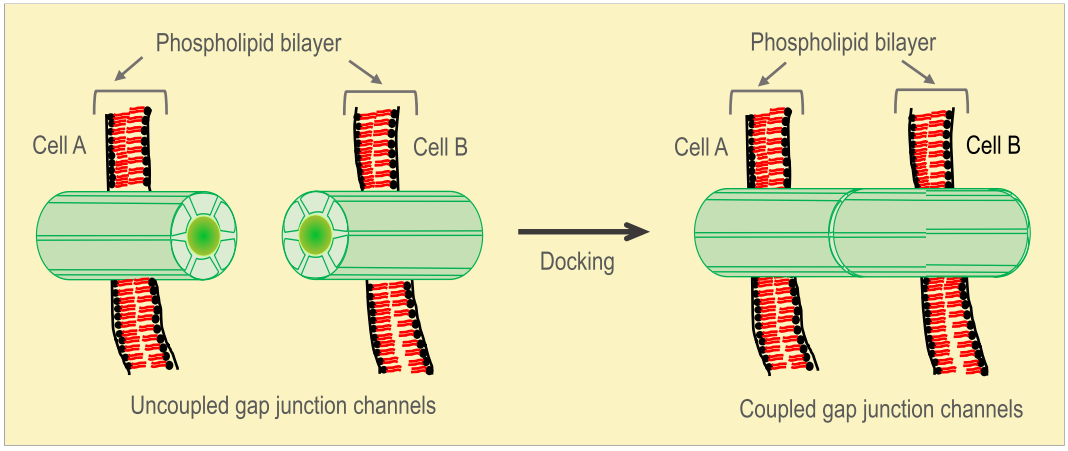

Fig. 2. Docking of connexons leads to coupled junctions. Gap junction intercellular communication is dependent on successful docking of two connexons located on two adjacent cells. When connexons present on the cell surface of one cell dock with connexons present on the cell surface of an adjacent cell it can lead to interlocking of the extracellular domains of each connexon allowing the formation of a gap junction connexin channel between two adjacent cells. These channels allow exchange of small molecules and ions permitting cell to cell communication.

2.1. Homotypic and heterotypic gap junctions

Hemichannels consisting of one connexin isoform are referred to as homomeric, while hemichannels formed from multiple connexin isoforms are referred to as heteromeric. The docking of two identical hemichannels results in a homotypic gap junction, whereas the docking of two non-identical hemichannels results in a heterotypic gap junction (Cottrell & Burt, 2005). Both homotypic and heterotypic gap junctions are implicated in disease processes. The physiological properties of heterotypic channels in which the 12 subunits are not the same connexin, differ in their properties of intercellular communication. There are several reports of intercellular channels that are formed from heterotypic connexins including in the retina, glial cells in the CNS, cardiomyocytes, and HeLa cells (Altevogt & Paul, 2004; Guldenagel et al., 2000; Martinez, Hayrapetyan, Moreno, & Beyer, 2002; Severs et al., 2004; Sohl, Guldenagel, Traub, & Willecke, 2000). In the retinal vascular cells, Cx43 is abundantly present but Cx37 and Cx40 are also expressed. In different tissues including retina, heterotypic gap junctions have been reported to be present involving Cx37, Cx40, and Cx43.

3. Connexin expression in different retinal cell types

Various types of connexins are expressed in the retina including Cx37 (Guldenagel et al., 2000), Cx40 (Matesic, Tillen, & Sitaramayya, 2003), Cx43 (De Maio et al., 2002), and Cx30.2 (Manasson, Tien, Moore, Kumar, & Roy, 2013) which are associated with the retinal microvasculature. Aside from these specific vascular connexins, the other types of connexins, which are localized and distributed in different retinal cell types are summarized in Tables 1 and 2. Of the three connexins, Cx37, Cx40, and Cx43 that are present on retinal endothelial cells and pericytes, Cx43 is the most abundant type (Janssen-Bienhold, Dermietzel, & Weiler, 1998). Reduced GJIC in vascular cells of the retina have been shown to affect non-vascular cells such as retinal astrocytes and Müller

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