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Expression and role of connexin-based gap junctions in pulmonary inflammatory diseases

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ABSTRACT

Connexins are transmembrane proteins that can generate intercellular communication channels known as gap junctions. They contribute to the direct movement of ions and larger cytoplasmic solutes between various cell types. In the lung, connexins participate in a variety of physiological functions, such as tissue homeostasis and host defence. In addition, emerging evidence supports a role for connexins in various pulmonary inflammatory diseases, such as asthma, pulmonary hypertension, acute lung injury, lung fibrosis or cystic fibrosis. In these diseases, the altered expression of connexins leads to disruption of normal intercellular communication pathways, thus contributing to various pathophysiological aspects, such as inflammation or tissue altered reactivity and remodeling. The present review describes connexin structure and organization in gap junctions. It focuses on connexins in the lung, including pulmonary bronchial and arterial beds, by looking at their expression, regulation and physiological functions. This work also addresses the issue of connexin expression alteration in various pulmonary inflammatory diseases and describes how targeting connexin-based gap junctions with pharmacological tools, synthetic blocking peptides or genetic approaches, may open new therapeutic perspectives in the treatment of these diseases.

Contents

Abbreviations: ADMA, asymmetric dimethylarginine; cAMP, cyclic adenosine monophosphate; CD73, cluster of differentiation 73; CDC2, cell division cycle 2; CFTR, cystic fibrosis transmembrane conductance regulator; cGMP, cyclic guanosine monophosphate; CH, chronic hypoxia; CH rats, rats subjected to chronic hypoxia; CK1, casein kinase 1; Cx, connexin; HPV, hypoxic pulmonary vasoconstriction; IP_3, inositol triphosphate; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MCT, monocrotaline; MCT rats, rats treated with MCT; MEF2, myocyte enhancer factor2; NF-κB, nuclear factor-κB; NO, nitric oxide; PAEC, pulmonary artery endothelial cells; PAH, pulmonary arterial hypertension; PASMC, pulmonary artery smooth muscle cells; PDE5, phosphodiesterase 5; PH, pulmonary hypertension; PKA, protein kinase A; PKC, protein kinase C; ROS, reactive oxygen species; shRNA, short hairpin RNA; siRNA, short interfering RNA; Th2, T helper cell 2; TNF-α, tumor necrosis factor-α; TGF-β, transforming growth factor-β; VE-cadherin, vascular endothelial-cadherin; ZO, zonula occludens; 5-HT, 5-hydroxytryptamine or serotonin.

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1. Introduction

Intercellular communications are essential to coordinate cellular responses in tissues and organs, thereby fulfilling an essential role in the spreading of signaling, survival, and death processes. In the present review, we are going to describe the presence and the role of such cell-to-cell communications based on intercellular communication channels known as gap junctions in the lung, including pulmonary bronchial and arterial beds, under physiological conditions. We are also going to address the role of these channels in lung inflammatory diseases. Indeed, because of the presence of numerous xenobiotic factors in the air such as dust, pollen, chemicals, airborne particulate matter and pathogens, several lung diseases are inflammatory disease types, inflammation being an ultimate host defense mechanism. Here, we are going to focus on lung inflammatory diseases in which the role of intercellular communications has already been pointed out (i.e. acute lung injury, asthma, cystic fibrosis, lung fibrosis and pulmonary hypertension). Consequently we are going to address the issue of the potential therapeutic interest to target such intercellular communications in the lung.

2. Structure of connexins, connexons and gap junctions

Intercellular channels or gap junctions (GJ) are transmembrane channels expressed on the surface of two neighboring cells allowing direct communication between the cytoplasms of both cells. GJ are formed by connexins (Cxs), transmembrane proteins that play a pivotal role in the direct movement of ions and larger cytoplasmic solutes between cells from various tissues. The Cx gene family comprises 20 members in human whereas there are 21 members in mice, 19 of which can be grouped as sequence-orthologous pairs (Sohl & Willecke, 2004). Each connexin contains four transmembrane domains (M1, M2, M3 and M4), two extracellular loops (E1 and E2), one intracellular loop (IL) and the amino and carboxy-terminus parts (NT and CT respectively) that are intracellular (Fig. 1A). The extracellular loops E1

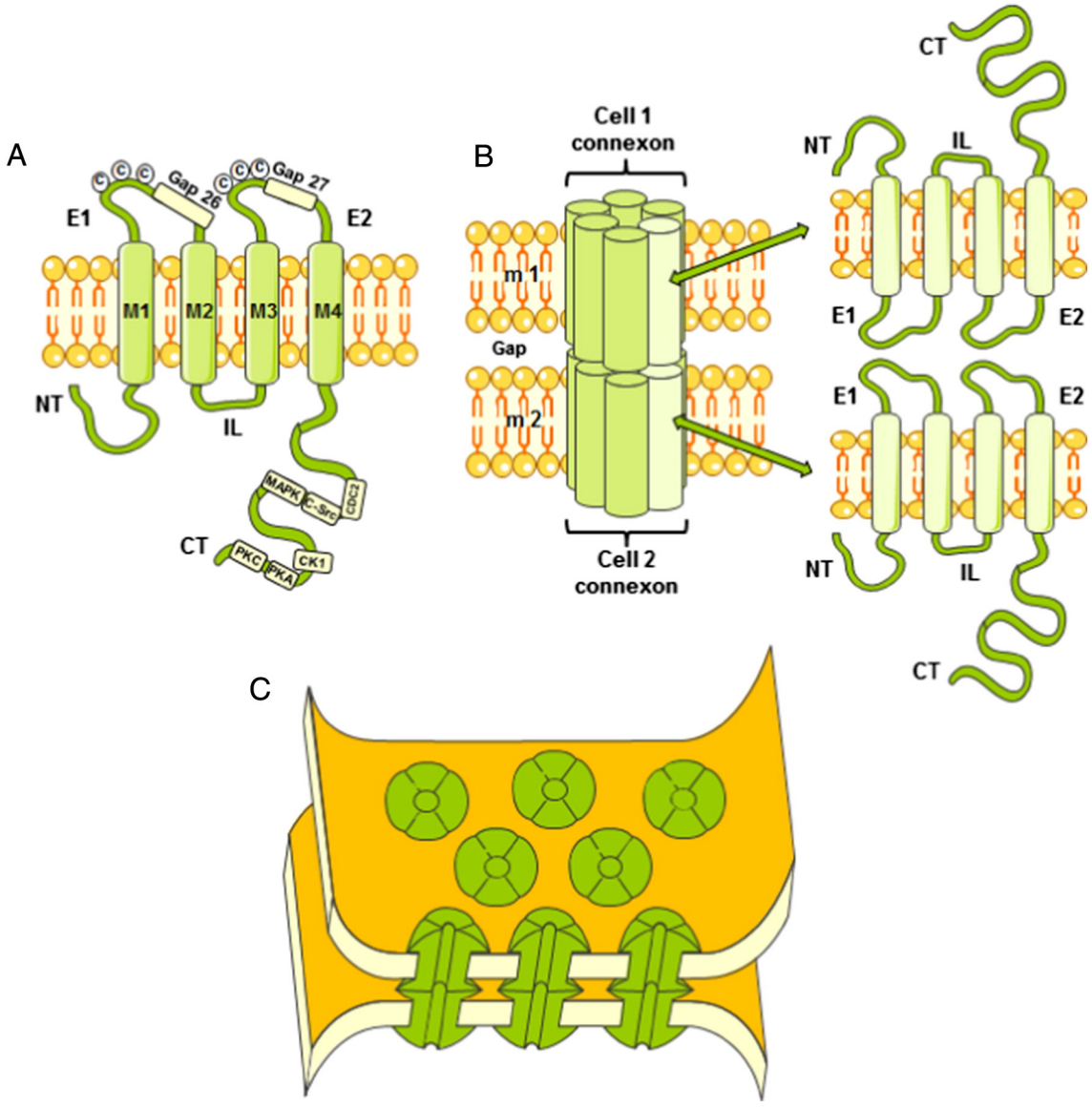

Fig. 1. Connexin structure and organization of a gap junction and of a junctional plaque. All connexins (Cxs) share a similar structure with 4 transmembrane domains (M1 to M4), two extracellular loops (E1 and E2), one intracellular loop (IL) and intracellular amino and carboxy-terminus parts (NT and CT respectively) (**A**). The Cx-mimetic blocking peptides Gap26 and Gap27 are going to fix E1 and E2 respectively (**A**). Cx regulation is mainly due to phosphorylations by protein kinase C (PKC), protein kinase A (PKA), casein kinase 1 (CK1), mitogen-activated protein kinases (MAPK), Src kinase (c-Src) and cell division cycle 2 (CDC2) on the CT part (**A**). **B** shows the two hexameric connexons from two adjacent cells (m 1 is the membrane of the cell 1 and m 2 the membrane of the cell 2). The two connexons are thus going to form a gap junction (GJ) via disulfide bridges between the three cysteine residues (©) on the E1 and E2 loops (**A** and **B**). **C** shows a gap junctional plaque.

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