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Review

Cell membrane permeabilization via connexin hemichannels in living and dying cells

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ABSTRACT

Vertebrate cells that express connexins likely express connexin hemichannels (Cx HCs) at their surface. In diverse cell types, surface Cx HCs can open to serve as a diffusional exchange pathway for ions and small molecules across the cell membrane. Most cells, if not all, also express pannexins that form hemichannels and increase the cell membrane permeability but are not addressed in this review. To date, most characterizations of Cx HCs have utilized cultured cells under resting conditions have and revealed low open probability and unitary conductance close to double that of the corresponding gap junction channels. In addition, the cell membrane permeability through Cx HCs can be markedly affected within seconds to minutes by various changes in the intra and/or extracellular microenvironment (i.e., pH, pCa, redox state, transmembrane voltage and intracellular regulatory proteins) that affect levels, open probability and/or (single channel) permeability of Cx HC. Net increase or decrease in membrane permeability could result from the simultaneous interaction of different mechanisms that affect hemichannels. The permeability of Cx HCs is controlled by complex signaling cascades showing connexin, cell and cell stage dependency. Changes in membrane permeability via hemichannels can have positive consequences in some cells (mainly in healthy cells), whereas in others (mainly in cells affected by acquired and/or genetic diseases) hemichannel activation can be detrimental.

Contents

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Introduction

Connexin hemichannels (Cx HCs)

Connexin hemichannels are hexameric oligomers of transmembrane proteins termed connexins (Fig. 1), and docking of two hemichannels in apposed membranes forms intercellular gap junction channels. When open at the unapposed cell surface, non-junctional hemichannels are aqueous pores (Fig. 1) permeable to ions and small molecules that allow diffusional exchange between the intra and extracellular compartments and also constitute a route for autocrine/paracrine cellular communication [1,2]. Cx HCs and gap junction channels frequently are oppositely influenced by various experimental and physiological conditions [3–8].

Although synthesis and trafficking pathways of Cx HCs might differ from those of intercellular channels, hemichannels formed by most studied connexins (all but Cx26 [9]) oligomerize in the Golgi/trans-Golgi network [10–13]. Upon assembly, hemichannels (except Cx26 HCs [9]) are transported to the non-junctional plasma membrane via a cytoskeleton-mediated route [14–16]. Once inserted in the plasma membrane, they diffuse laterally to join the external aspect of gap junctional plaques [17,18], where they dock with hemichannels from a neighboring cell to form intercellular channels. However, Cx43 HCs may also be directly targeted to the region where gap junctional plaques are found via a microtubule/dynein/β-catenin/N-cadherin-dependent pathway [19]. It might be possible that hemichannels in non-junctional membrane and those in gap junctions are derived from different precursor pools. In support of this notion, fluorescent-tagged Cx43 can be delivered to cell protrusions or to cell surface domains that lack a contacting cell [20].

In cells expressing wild-type connexins, changes in surface hemichannel levels and/or intrinsic properties of hemichannels

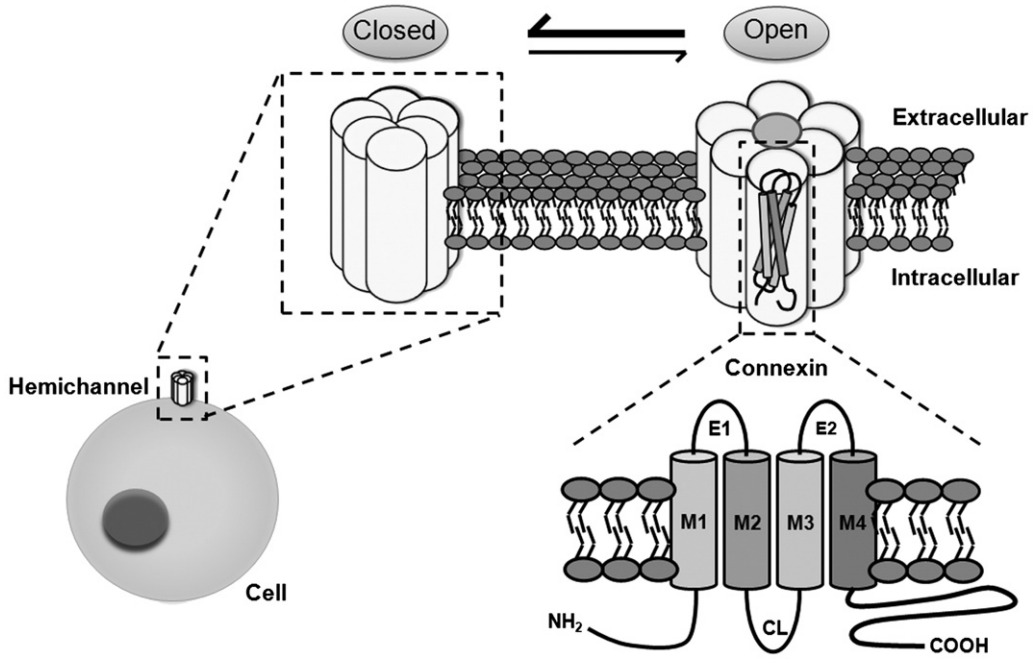

Fig. 1 – Diagram illustrating basic structures of connexins and undocked hemichannels present at the cell surface. The membrane topology of a connexin consists of 4 membrane-spanning domains (M1-M4), 2 extracellular loops (E1 and E2) and 1 cytoplasmic loop (CL). The amino (−NH_2) and carboxy (−COOH) terminal tail are intracellular. A hemichannel is formed by six connexins that oligomerize laterally leaving a central pore. In cultured cells under resting conditions hemichannels remain preferentially closed, but they can be activated by diverse physiological and pathological conditions, offering a diffusional transmembrane route between the intra and extracellular milieus.