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Sommario/riassunto	Coordinated cell interactions are required to accomplish several complex and dynamic tasks observed in several tissues. Cell function may be coordinated by cell-to-cell communication through gap junctions channels (GJCs). These channels are formed by the serial docking of two hemichannels, which in turn are formed by six protein subunits called connexins (Cxs). It is well known that GJCs are involved in several functions, such as intercellular propagation of calcium waves, spread of electrotonic potentials and spatial buffering of ions and metabolites. On the other hand, undocked hemichannels, which are not forming GJCs, can also serve other functions as “free hemichannels”. Currently, it is recognized that undocked hemichannels may have functional relevance in cell physiology allowing diffusional exchange of ions and small molecules between intra- and extra-cellular compartments. Additionally, another family of proteins calls pannexins (Panx) also forms functional hemichannels at the plasma membrane. Recently, Panxhemichannels have been involved in both pathological and physiological processes. Controlled hemichannel opening allows

the release of small signaling molecules including ATP, glutamate, NAD+, adenosine, cyclic nucleotides, PGE2. They also allow uptake of relevant signaling molecules (e.g., cADPR) and metabolites (e.g., glucose). Additionally, a growing body of evidence shows that hemichannels are involved in important processes, such glucose detection in tanicytes, activation of the inflammasome, memory consolidation in the basolateral amygdala, potentiation of muscle contraction and release of nitric oxide from endothelial cells, among others. However, hemichannels can also play an important role in the homeostatic imbalance observed in diverse chronic diseases. In fact, massive and/or uncontrolled hemichannel opening induces or accelerates cell death in several pathological conditions including Charcot-Marie-Tooth disease, ischemia, oculodentodigital dysplasia, hydrotic ectodermic dysplasia, inflammatory responses, and deafness. Hemichannel-mediated cell death is due mainly to an entry of Ca+2. The latter activates proteases, nucleases and lipases, causing irreversible cell damage. An increasing amount of evidence demonstrates that blockade of uncontrolled hemichannel opening greatly reduces the cellular damage observed in several chronic diseases models. Therefore, Cx and Panx-hemichannels appear as promising drug targets for clinical treatment of human chronic diseases. Therefore, pharmacological tools are urgently needed to further elucidate hemichannels functions and to validate them as drug targets for the development of novel therapies for connexin-based diseases. Thus, understanding the role of Cx and Panx-hemichannels under physiological conditions and recognizing the molecular mechanisms controlling them, may provide us with a better picture of the hemichannels participation in some diseases and of the signals underlying their malfunctioning.