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Editorial

The Connexins, Part III

In animal tissues, most cells are connected via intercellular cytoplasmic channels clustered in plasma membrane spatial microdomains termed gap junctions, which allow cells to directly exchange ions and small molecules. Each channel results from the docking of two half channels, which are hexameric torus of junctional proteins around an aqueous pore. All junctional channels have a similar overall structure but, unlike many other membrane channels, different gene families encode the membrane proteins that form them in different animal phyla, as summarised in the Preface [1]. The connexin family, abundantly expressed in vertebrates but also present in invertebrate chordates, is by far the most documented of the junctional proteins. The present issue of *Biochimica et Biophysica Acta Biomembranes,* the last of three parts, is designed to summarize some of the new information on some of the characteristics, properties and roles of connexin-made structures and some consequences of their dysfunction.

Each connexin shows tissue-or cell-type-specific expression, and most organs and many cell types express more than one connexin. Some of the connexins (e.g., Cx32 or Cx43) are present in many cell types, but some others are only expressed in very limited organs and cells. Even in the same tissue, the expression pattern of each connexin shows cell-type specificity and developmental changes, suggesting the presence of distinct but tight control mechanisms for regulation of connexin gene expression. Oyamada et al. [2] summarize recent developments on transcriptional regulation of connexin genes.

Phosphorylation, a widespread post-translational modification of proteins, is a primary means of mediating signal transduction events that control numerous cellular processes via a highly regulated dynamic interplay of protein kinases and protein phosphatases. King and Lampe [3] focus their attention on the dynamic regulation of the phosphorylation status of Cx43 (the most widely expressed and abundant connexin) in tissues and how these regulatory events are affected during development, wound healing, and carcinogenesis.

Different approaches (e.g., the use of gene knockouts) have yielded some information on the diverse functions of connexins, but there is a pressing need for potent and specific pharmacological agents directed at them. Most of the junctional channel pharmacology arose from testing reagents known to target protein kinases or other ion channels, or by accident when researchers were investigating other intracellular pathways that may regulate the activity of these channels. If selective agents have not yet be produced, taking advantage of emerging structural information and of the increasing knowledge of the biophysical properties of these channels, some promising compounds and strategies have begun to emerge, summarized by Salameh and Dhein [4].

The embryonic development of the brain and the subsequent maturation of specific brain areas are an evolving process which involves a diversity of mechanisms, including gap junction-mediated coupling between developing neurons as well as developing glial cells. Interconnected cells form clusters which can be considered as communication compartments in which the information transfer is mediated electrically by ionic currents and/or chemically by, e.g., small second messenger molecules. Sutor and Hagerty [5] evaluate the significance of gap junction-mediated cell coupling during the maturation of the neocortex.

The skeleton is a dynamic tissue that constantly undergoes continuous remodelling in which osteoclasts resorb aged or damaged bone, leaving space for osteoblasts to make new bone. These cells constantly receive signals from adjacent cells, hormones, and bone matrix that regulate their proliferation, activity, and survival, and gap junctional communication has been hypothesized to play a critical role in the coordination of bone remodelling; Stains and Civitelli [6] summarize recent findings which have elucidated some of the roles of gap junctions in bone development and maintenance.

Most endocrine and exocrine secretions are multicellular events which depend on the coordinated activity of numerous cells, achieved in a variety of ways which, with evolution, have been progressively integrated into a complex regulatory network that allows individual cells to sense the state of activity of their neighbours and to regulate, accordingly, their own level of functioning. Michon et al. [7] present an overview of compelling evidence for a central role of gap junctional channels in the function of both endocrine and exocrine glands.

Gap junctional communication appears to play major roles in several functions of the male reproductive tract, including germ cell proliferation and differentiation as well as in modulating the initiation and maintenance of smooth muscle tone in different structures. Pointis et al. [8] overview the

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current knowledge available concerning the identification of connexins, their distribution in the testis and in different structures of the male genital tract (epididymis, seminal vesicle, prostate, corpus cavernosum), their crucial role in the control of spermatogenesis and their implication in the function of the male accessory glands, including functional smooth muscle tone.

In the female reproductive tract, the successful implantation requires a close interaction between the embryo and the uterus. Direct cell-cell communication via junctional channels seems to play important roles in the preparation of the uterus for embryo implantation and in the regulation of trophoblast invasion. Malassiné and Cronier [9] present the diversity of placental structures throughout the mammalian species and overview the expression, the localisation and the possible roles of connexins and of gap junctional communication in placental functions and development of the different placental types.

Given their key roles in homeostatic control, connexins and their channels are frequently targeted upon impairment of this critical balance, and this notion has been extensively described in the case of carcinogenesis. Despite the many exceptions that have been reported, tumour cells generally display reduced gap junctional coupling. Numerous mechanisms appear involved, including the (relatively rare) occurrence of mutations in connexin genes, epigenetic modifications (DNA hypermethylation for example) able to trigger silencing of connexin gene expression, inappropriate phosphorylation and aberrant cytosolic localization of connexins. The loss of cell-to-cell junctional communication would allow tumour cells to escape from normal growth regulation by the surrounding cells, thereby representing their growth independence. Mesnil et al. [10] overview the data on the possible links existing between alterations of gap-junctional intercellular communication capacity and the stages of cancer progression in various cancer models. King and Bertram [11] discuss the possibility of connexins as potential anti-oncogenic targets for chemoprevention and/or chemotherapy and also for exploitation in chemotherapy through the “bystander” effect.

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Jean-Claude Hervé
Interactions et Communications Cellulaires,
UMR CNRS 6187, PBS, 40 avenue du R. Pineau,
86022 POITIERS Cédex, France