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Introduction

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This set of nine minireviews provides overviews of some of the changing and exciting directions of current gap junction research. The subjects covered in these minireviews encompass a broad spectrum of research on molecular and cellular structure, molecular and cellular physiology, signal transduction, hormonal regulation, and development. Nevertheless, the areas covered are selective rather than comprehensive since to cover the whole gap junction field would require more than nine reviews.

The term "gap junction" originated from the first histology studies in the late 1950's and is used to describe a cell–cell contact area in which the two plasma membranes from apposing tissue cells come close together but do not fuse. Staining of the cells enhanced the appearance of a space or "gap" between the two membranes and also delineated the channel structures in the two membranes. The pre-1985 classic textbook summary of a gap junction describes a static structure composed of aggregates of membrane channels. These membrane channels were thought to contain subunits of a ubiquitous protein which formed two apposing hexamers in the two membranes. In this classic description, the gap junction sits alone in the cell membrane with its pore providing a passageway between cells for any molecule of molecular weight less than 1000 Daltons.

Between 1986 and 1989, cloning of gap junction proteins showed that there is not just one type of gap junction protein (or connexin) but a multigene family of proteins. At the time of writing, approximately 14–18 connexins have been sequenced. Following the identification of different connexin sequences came structure–function studies which tested the ability of expressed connexin proteins to form functional channels in expression systems. These expression systems have provided a way to investigate gap junction membrane channels that are composed of more than one connexin isoform and have caused gap junction researchers to reevaluate our ideas about the regulation of gap junction expression.

The minireview series starts with an article on the structure of gap junctions by Sosinsky. This article describes the structure of the gap junction as it is currently known and relates this structure to published molecular biology and mutagenesis studies. Also presented in this review is an overview of the cellular structure of gap junctions. This overview describes the arrangement of the membrane channels *in vivo* and the way in which the expression of multiple connexins within cell types may influence the packing of the membrane channels in gap junction plaques and nonjunctional areas.

Gap junction proteins are actually dynamic structures that exhibit a fast turnover in cells (often with less than a 6 hour half-life). Therefore, trafficking and oligomerization of the channels before they are inserted into the plasma membrane must be highly regulated. In addition, since turnover is rapid, the fast degradation of gap junction structure or connexins must be also regulated. The minireview by Laird details the present state of knowledge of gap junction assembly and disassembly and gives a step-by-step account of the life cycle of a gap junction protein.

The review by Willecke and Haubrich provides an evaluation of the different systems that have been used to express gap junction proteins. Willecke and Haubrich describe how these studies relate to what is known about the function of gap junctions in tissues. In addition, Willecke and Haubrich present state-of-the-art studies involving transgenic mice in which connexin genes have been obliterated or "knocked out." These transgenic mice are being used as a new expression system for probing how missing connexin genes influence animal development and organ physiology.

There are three articles in this issue on the molecular physiology of gap junction membrane channels. However, each article has a different focus. Both Brink

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and Veenstra use the term "selective permeability" to describe the properties of the gap junction pore. These three reviews are intended to show that the classic idea that the gap junction provides a nonselective channel for small molecules is not correct. Furthermore, the discovery that multiple connexin isoforms are expressed within a single cell type also complicates the picture of molecular permeability.

The recent studies reviewed by Veenstra show that, in spite of the conservation of the channel-forming domains, the selectivity and functional pore size does vary between the different connexin isoforms. In his review, Veenstra presents a guide to the relative permeabilities found between different connexins and discusses changing ideas on channel conductance and ionic permeability and selectivity. These properties are explored in the context of the connexin sequence differences.

In the second review on molecular physiology, White and Bruzzone describe studies in which gap junctions form between cells containing different types of connexins. This pairing can occur because the sequence in the extracellular domains is highly conserved. However, what is surprising is that the connexin family displays rules of selectivity for functional expression between different isoforms (in short: "who talks to whom"). The mixed channels may have distinct physiological roles since homotypic junctions (containing a single connexin isoform) have distinctive physiological properties from heterotypic junctions (containing more than one connexin isoform). White and Bruzzone explain how these rules of selectivity may be determined by the sequences found in the extracellular domains.

Because of the relevance of their work to X-linked Charcot–Marie–Tooth syndrome (a degenerative neuropathy of the peripherial nervous system caused by defects in connexin32), gap junction researchers have been reevaluating the role that gap junctions play in the nervous system. The review by Brink describes the state of knowledge of the molecular physiology of gap junction channels in excitable tissues. Gap junctions are found to play important roles in regulating the transmission of electrical impulses. Both Brink and Veenstra describe how the main purpose of gap junction channels may be to pass small charged second messengers, again changing previous ideas of their roles in cellular processes.

The idea that gap junctions act as stand-alone structures has also been changing. Recent work has shown that gap junctions are targets of growth factors and oncogenes as well as interacting with cell adhesion molecules such as cadherins. Lau *et al.* describes evidence for the involvement of gap junctions, in particular connexin43, in signal transduction pathways. Phosphorylation and dephosphorylation of connexins may provide an additional regulatory role in cell growth and oncogenesis.

The review by Meda describes the role of gap junctional intercellular communication in hormonal secretion and regulation. Gap junctions are abundant in exocrine and endocrine glands, suggesting that maintenance of these structures is necessary for proper functioning. This review describes how differential expression of connexins is important at the organ level.

Lastly, intercellular communication is a fundamental process in development. Breakdown of gap junctional communication leads to developmental defects as seen in the cardiac malformations of viscerohypertaxia patients. It has long been known that parts of embryos are linked by gap junctions into units called communication compartments. The review by Lo presents the current knowledge about the role of gap junctions in development and describes recent work on the temporal-spatial pattern of expression of connexin isoforms. Lo describes how disruptions or changes in this temporal–spatial pattern can lead to abnormal embryogenesis in animal model systems.

In summary, the authors of this volume and I hope to leave the non-gap junction community with our excitement and enthusiasm for the breadth of the field of gap junction research. We hope to leave the reader with the impression that many of our original notions about gap junctions are changing. I personally thank all the contributors to this volume. I also wish to thank Linda Musil, Guy Perkins, and Lucas Buehler for their discussions and suggestions during the planning and execution of this minireview series.