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Preface

The apical junctional complexes, roles, and dysfunctions

In multicellular organisms, epithelial barriers, which promote organ homeostasis by restricting the flow of ions and solutes between cells, are fundamental to the physiology of organ systems. Epithelia form diffusion barriers between cellular compartments of very different fluid and solute composition through both asymmetrically distributed transcellular transport mechanisms (transcellular pathway) and also by structures that regulate the diffusion of ions and small, noncharged solutes through the paracellular pathway. At the apical end of the paracellular space, adjacent cell membranes are indeed in close apposition, a site that was termed by early anatomists as the "terminal bar." These intercellular junctional complexes are composed of the tight junctions or zonula occludens, the adherens junctions or zonula adherens, and desmosomes or macular adherens, whereas gap junctions provide for intercellular communication. Tight junctions (TJs) form an intercellular diffusion gate regulating the passage of ions, water, and various macromolecules through the paracellular spaces, and a fence restricting the apical/basolateral diffusion of membrane proteins and lipids whereas adherens junctions and desmosomes link membrane and cytoskeletal components at discrete contact regions. The present issue of *Biochimica et Biophysica Acta* "Biomembranes" and the companion issue "The apical junctional complexes, composition, structure and characteristics" (Biochim. Biophys. Acta 1778 (3), 2008) were designed to summarize the main aspects of the state of the art on the characteristics, composition, structure, and roles of the apical junctional complexes as well as some of the consequences of their dysfunctions.

The polarized architecture of epithelial cells and tissues is a fundamental determinant of animal anatomy and physiology, and mammalian epithelial tumors for example appear to lose polarity as they progress toward malignancy. *Drosophila melanogaster* is a genetically simple model, particularly suited to examine how a proper epithelial architecture is intimately involved in a cell's ability to control its growth. Badouel and McNeill [1] explore the links between growth and apical junction proteins in the regulation of growth control in this model.

Several submembranous components of apical junctional complexes are able to influence gene expression through their nuclear shuttling or their specific binding to transcription factors. Balda and Matter [2] describe how tight junction proteins participate in the regulation of gene expression and cell proliferation, as well as how they are regulated themselves by different mechanisms involved in gene expression and cell differentiation. Tight-junction-associated signaling pathways are deregulated in cancer cells but whether these changes are a cause or consequence of transformation remains to be elucidated.

The different types of intercellular junctions (tight, anchoring and gap junctions), sharing common adaptor molecules (particularly zonula occludens-1), frequently present intermingled relationships, their proteins coassemble into macromolecular complexes, and their expressions are coordinately regulated. Derangeon et al. [3] present an overview of these intimate spatial relationships between the different types of junctions (well conserved through evolution) and highlight the physiological importance of such protein–protein interactions in intercellular junction functions.

Integrins comprise a large family of cell adhesion molecules that mediate interactions between the extracellular environment and the cytoplasm. The analysis of the expression and functions of these molecules has revealed their importance in the regulation of many aspects of cell behavior, including cell death, proliferation, migration, and differentiation. Johnson et al. [4] summarize the current understanding of integrin involvement in skeletal muscle formation and discuss what conclusions can be drawn about integrin function by studying the evolutionary conservation of integrins.

Small GTP-binding proteins (G proteins) are molecular switches that control a wide variety of signal transduction pathways in all eukaryotic cells. More than 100 small G proteins have been identified, with slightly different structures and mechanisms of action. They are classified into several main families (Ras, Rho, Rab, Rap, Arf, Ran, Rheb, Rad, and Rit), each of which being further divided into subfamilies. Pannekoek et al. [5] highlight the latest findings on the Rap signaling network in both *de novo* formation and dynamic regulation of intercellular junctions, where several Rap guanine nucleotide exchange factors (RapGEFs) function to activate Rap. Popoff and Geny [6] examine the important roles played by Rho/Ras GTPase in the regulation of TJs via the contraction of apical acto-myosin filaments and of Rac/Cdc42 in the coordination of assembly-disassembly of AJ components, and the reciprocal influence on the integrity of intercellular junctions on the activities of G-proteins, particularly Rho-GTPases.

TJ functions are essential for the development and physiological functions of organs but appropriate experimental methods to investigate their *in vivo* importance were lacking until their molecular components were identified. Targeted gene inactivations (commonly known as gene knockout) are currently employed to study the functional importance of specific genes and proteins and the impact of specific genetic mutations and deletions on complex metabolic processes and their involvement in various diseases. Furuse [7] summarizes the available data on pathologies of knockout or knockdown mice and natural mutations of the genes of TJ-associated structural proteins and discusses the roles of TJs *in vivo*.

In epithelial and endothelial cells, the term "polarity" refers to an asymmetric distribution of macromolecules (proteins, lipids and carbohydrates) within a cell resulting in the plasma membrane to the subdivision into apical and basolateral domains and, within each of these domains, by the existence of smaller, submicrometer-sized, domains formed by segregation of plasma membrane proteins and lipids. Giepmans and van Ijzendoorn [8] overview the functional interrelationship between these diverse plasma membrane microdomains and their formation, and address emerging cross-talk between

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junctional microdomains to establish and maintain epithelial cell polarity and architecture.

Epithelia constitute one of the primary physical barriers that protect the organism against infectious agents in the environment. Their integrity is maintained by intercellular junctional complexes whose number of components are targets and/or receptors for factors expressed and/or released by viruses, bacteria, or parasites to alter the structure and function of the TJ barrier, to induce fluid and electrolyte secretion, or to activate the inflammatory cascade, for example. Guttman and Finlay [9] overview the clever strategies developed by these pathogens to bypass the TJ barrier. At the same time, specific strategies used by pathogens and their virulence factors represent very useful tools to identify novel TJ protein functions.

The blood-brain barrier (BBB), formed by the endothelial cells that line cerebral microvessels, plays important roles in maintaining a precisely regulated microenvironment for reliable neuronal signaling. Any minor defect or imbalance of the BBB integrity is known to result in serious maladies with important social impacts (e.g., multiple sclerosis, stroke, brain tumors, epilepsy, or Alzheimer's disease). Weiss et al. [10] focus on the implication of brain endothelial tight junctions in BBB architecture and physiology, discuss the consequences of BBB dysfunction in these CNS diseases, and present some therapeutic strategies for drug delivery to the brain across the BBB.

The major role of the renal tubule is to alter the volume and composition of the glomerular filtrate in accordance with the homeostatic needs of the body, thereby transforming tubular fluid into urine. The nephron exhibits considerable heterogeneity in the permeability properties of its different segments, mainly determined by a class of transmembrane proteins known as claudins, which form both the barrier and the pore of the paracellular pathway. Balkovetz [11] discusses early observations of renal tubule paracellular transport and more recent information on the discovery of the claudin associated membrane proteins and how they relate to normal renal function as well as diseases of the human kidney.

TJs represent diffusion barrier by tight control of the transcellular and paracellular pathways; this is accomplished by asymmetrical distribution of transporters and channels for the transcellular route, and by regulation of diffusion through the paracellular space via the formation of ion selective pores within the TJ strands. Many cytokines have been shown to influence epithelial and endothelial TJ function and the actin cytoskeleton both *in vivo* and *in vitro*. Capaldo and Nusrat [12] provide an overview of the influence of cytokines on TJ functions, of their contribution to different pathologic conditions, and of the involved molecular mechanisms.

Cancers encompass a broad category of diseases that arise as a result of the accumulation of mutations, chromosomal instabilities, and epigenetic changes that together impair the cell's system of cell growth and death. An important step in the formation of cancer metastases is interaction and penetration of the vascular endothelium by dissociated cancer cells. TJs are therefore the first barrier that cancer cells must overcome in order to metastasize. Martin and Jiang [13] summarize the recent progress in elucidating the role of TJ in the invasion and metastasis of cancer via changes in barrier function due to modulations in the expression of TJ proteins and alterations in the structure of the TJ itself.

Therapeutic agents frequently need, in order to reach their target, to cross epithelial and endothelial barriers via either transcellular or paracellular pathways. The former is taken by lipophilic drugs and by molecules selectively transported by channels, pumps, and carriers present in the plasma membrane whereas hydrophilic molecules, unable to cross biological membranes, have their paracellular flux markedly limited. Deli [14] presents the methods, molecules, and excipients investigated for the safe and reversible opening of these junctions to enhance drug absorption and penetration. For a long time, low efficiency and high toxicity prevented these approaches to be useful for pharmaceutical therapy but new TJ modulators, designed to directly interact with TJ proteins or regulating molecules, are promising candidates to improve drug delivery.

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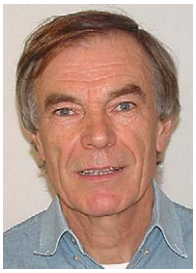

Jean Claude Hervé received his Ph.D. from the Department of Physiology, University of Poitiers (France) in 1984, where he worked as a National Centre for Scientific Research (CNRS) researcher, and then spent two years as a postdoctoral fellow at the Laboratory of Physiology of University of Oxford (UK) before joining the Institute of Physiology and Cell Biology of the University of Poitiers. His current research focuses mainly on the modulation of the direct cell-to-cell communication via gap junctional intercellular channels, finely tuned by the metabolic state of communicating cells and by humoral factors. Jean Claude also served as an executive guest editor of several international journals, among them *Biochimica Biophysica Acta*, *Progress in Biophysics and Molecular Biology*, *Current Pharmaceutical Design*, *Biology of the Cell*, and *Mini-Review in Medicinal Chemistry*. Academic Societies: the Physiological Society, the American Physiological Society.