American Journal of Physiology-Cell Physiology theme: ion channels and transporters in cancer

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IN THIS ISSUE, the American Journal of Physiology-Cell Physiology initiates the publication of a new Theme series of review articles that focus on the pathogenic role of ion channels and transporters in cancer. Ion channels, as an important family of membrane proteins that are highly expressed in virtually all types of cells, not only regulate cell excitability, muscle contraction, and glandular secretion. Activity of various ion channels in the plasma membrane and intracellular organelle membranes also plays an important role in regulating cell proliferation, migration, apoptosis and differentiation, cellular functions, and processes that are traditionally considered to be regulated by intracellular signaling proteins and transcription factors. We hope that this series of reviews will bring to readers a new concept regarding the potential role of ion channels in cancer and help provide a rationale for the targeting of ion channels and their chaperones as a new approach for the treatment of cancer.

A neoplasm as a result of neoplasia (from the Greek term meaning “new growth”), or the synonymous term “tumor” (from the Latin term meaning “swelling”), was defined by the British oncologist R. A. Willis in 1952 (2) as “an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissue, and persists in the same excessive manner after cessation of the stimulus which evoked the change.” The basic characteristic of tumor (or a neoplasm) is hence its abnormal “growth.” To understand tumor growth, we must not forget what Theodor Boveri, an eminent pathologist, wrote in 1914 (1): “When I published the results of my experiments on the development of double-fertilized sea-urchin eggs in 1902, I added the suggestion that malignant tumors might be the result of a certain abnormal condition of the chromosomes, which may arise from multipolar mitosis.”

Indeed the excessive and uncoordinated growth of tumors relies on the fact that cancer cells are mutants. They often carry somatic mutations of specific (most likely growth-related) genes, although other modifications possibly caused by epigenetic mechanisms, such as gene amplification or inactivation, can also occur. The systematic search for genes that are particularly susceptible to mutation during carcinogenesis has helped in showing that cancer is a multistep process, a concept that and is summarized in the notion of “tumor progression.”

The term “cancer,” synonymous of neoplasm (as a result of neoplasia) and tumor, more precisely includes the process of invading surrounding tissues by malignant cells during tumor progression. The concept of “cancer” as a multistep process involves the progressive (but sometimes via very rapid progression) acquisition of genetic alterations, leading to the setting of malignancy. In this process, the early steps may involve alterations of a relatively small number of genes implicated in cell proliferation, apoptosis, and differentiation. As a consequence, cell clones are produced that resist apoptosis and are capable of unlimited proliferation. However, the tumor mass is restrained in its growth by the lack of an appropriate blood supply (the lack of which can create hypoxia) and by the hindrance operated by the surrounding tissue. Both these impediments need to be overcome. Hence tumor cells promote angiogenesis and, at later stages, undergo genotypic (with new mutations/genetic alterations in different pathways) and phenotypic features are selected that enable cells to invade and colonize (metastasize) neighboring or even distant tissue and eventually to evade and overcome immune response.

The molecular dissection of neoplastic progression potentially opens the way to the development of drugs addressing tumor-specific processes. The many recent efforts devoted to this task have led to substantial improvement in treatment. For instance, novel selective inhibitors of tyrosine kinase receptors and non-receptor tyrosine kinases, pivotal regulators of cell survival and proliferation, as well as of the angiogenic process (e.g., inhibitors of vascular endothelial growth factor), have been developed for cancer treatment. By combining new targeted agents with traditional chemotherapy, survival of some patients can often be prolonged.

Ion channels and transporters in the plasma membrane (and intracellular organelle membranes) are an emerging class of molecules or proteins that may represent good targets for developing antineoplastic therapy. Why ion channels? First of all, their expression is often grossly altered in human cancers. Second, channel dysfunction can have a strong impact on cell function and signaling, with ensuing effects on cancer progression. Third, ion channels are a pharmaceutically tractable molecular class. A major advantage is their accessibility from the extracellular side. Thus the study of the role of ion channels in the different aspects of tumor progression has the potential to unravel new therapeutic approaches.

This Theme series includes articles in which renowned experts discuss current findings and progress on: 1) the functional role of ion channels (and transporters) in tumor cell proliferation, apoptosis, differentiation, and migration; 2) the role of ion channels in tumor cell-microenvironment cross talk; 3) the role of intracellular Ca2+ signaling in tumorigenesis and tumor angiogenesis; 4) the pathogenic role of ion channels and transporters in tumor progression; and 5) the role of ion

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channels and membrane potential in cancer stem cell proliferation.

There are more than 400 genes encoding ion channel subunits that regulate the flow of ions (e.g., Ca\(^{2+}\), Na\(^{+}\), K\(^{+}\), H\(^{+}\), Cl\(^{-}\), HCO\(_3\)^{-}\)) across the plasma membrane (and the intracellular organelle membrane). Many of the ion channel genes have been shown to play a critical role in the pathogenesis of various diseases including cancer. One of the grand challenges of ion channel research is to identify the specific subtype of ion channels that plays a pathogenic role in cancer (tumorigenesis, tumor progression, tumor metastasis, and tumor angiogenesis) and to develop specific blockers (and openers) for the channel as tumor suppressants.

The topic “Ion channels and transporters in cancer” is a broad field that fits in quite well with the mission of American Journal of Physiology-Cell Physiology. We invite your feedback about this series of review articles on this topic and sincerely encourage readers to submit original work on ion channels in cancer to the American Journal of Physiology-Cell Physiology.

DISCLOSURES
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REFERENCES