Foreword

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The given special issue of the journal *Biologicheskie Membrany* is dedicated to the intracellular signaling and includes a number of designated articles authored by attendees of the International Conference *Reception and Intracellular Signaling*, which was held in Pushchino on June 2–4, 2009. This conference is organized on the regular basis every two years and attracts Russian and foreign researchers, who are united, despite diverse fields of cellular biology they work in, by the common interest in intracellular signaling as such and in underlying molecular mechanisms. The conference covers many aspects of intracellular signaling, including general problems, signaling in electrically excitable and non-excitable cells, sensory transduction, a cellular stress response, and intracellular communications in plant cells, low eukaryotes, and prokaryotes.

Being a unicellular organism or operating in a multicellular tissue, a typical cell is subjected to influence of numerous physical and chemical factors from outside but responds specifically to the limited number of external stimuli. Different cells can react to the same external signal in distinct manners by altering membrane voltage or cellular morphology, increasing motility or a rate of metabolic processes, switching on/off expression of certain genes. All these diverse cellular responses are mediated by multiple receptors located on a cell surface and coupled to a variety of intracellular signaling cascades. It is hard to overestimate the importance of the fundamental and applied research of signaling systems, given particularly that many modern medical preparations were developed on the basis of current concept on receptors, agonists and antagonists, and using modulators of signaling proteins.

G-protein coupled receptors (GPCRs) occupy a specific niche in the receptor world. In diverse animals from invertebrates to mammals, GPCRs are encoded by multiple genes, comprising nearly 3% of the genome. It is hardly accidental that so significant fraction of the genome is designated for GPCRs, it is rather an indication of biological significance of these receptors. Indeed, GPCR-based signaling systems are characterized by high sensitivity and amplification

and simultaneously by deep adaptability, the feature allowing a cell to monitor external stimuli over a very wide range of intensities. These effective signaling systems are employed by sensory cells for transduction of light and odorous stimuli, they are involved in synaptic transmission tuning in neurons, GPCRs regulate contraction of muscle cells. In multicellular organisms, apparently all cells use GPCRs for monitoring hormones and other first messengers, i.e. molecules released by different cells to adjust their own cellular functions and frequently, to mediate paracrine regulations.

With few specific exceptions, including signaling with nuclear receptors, the term *intracellular signaling cascade* means the main pathway of signal spreading from a receptor in the plasma membrane to a targeted effector in various intracellular compartments. In many cases, consequent biochemical reactions direct an intracellular signal by producing second messengers, the rapidly diffusing molecules that regulate cellular functions locally or in a global manner. Second messengers, such as cAMP, IP₃, and Ca²⁺, may act in the cytoplasm, or they may diffuse in the plasma membrane, as is the case of diacylglycerol and phosphatidic acid, and regulate activity of membrane proteins. Very diverse signaling/regulatory processes, such as cellular metabolism tuning, olfactory transduction, or hormonal regulation, involve second messengers.

As was shown during the last decade, multiple signaling systems operating in cells are built as a sequence of protein kinases, wherein consequent phosphorylation activates the whole cascade. Evidence implicates at least four MAPK cascades in transduction of diverse extracellular signals, which initiate key intracellular processes, such as proliferation, differentiation, development, stress response, and apoptosis. The MAPK cascades include up to five levels of different kinases, which consequently phosphorylate one another. One more important signaling pathway known as the PKB cascade, which is a relatively new arrival to the signaling field, involves PI3 kinase phosphorylating phospholipid PIP₂ as well as a number of protein kinases,

including PDK1, PKB, and GSK3. The PKB cascade is basically involved in the stress response.

Naturally, the considered examples do not cover all known receptor systems and signaling pathways operating in cells, which are too diverse and complicated to be deeply considered in a single issue of a journal.

Nevertheless, taken together, the articles presented here provide an appropriate overview of many aspects of intracellular signaling and adequately reflect a level of studies that is maintained by Russian researchers in this bursting field.

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