Cell-to-cell interactions are essential for embryonic development and for a plethora of physiological processes in adulthood (e.g., wound healing). Along with hormones and neurotransmitters, growth factors are the major messengers of intercellular communication in mammals. Many growth factors bind trans-membrane receptors whose cytoplasmic domain initiates signaling by means of an intrinsic tyrosine kinase activity, and oncogenic processes often exploit growth factor signaling for malignant transformation. An example is provided by the ErbB family of receptors for the epidermal growth factor (EGF) and neuregulins: self-production of ligands (autocrine loops), truncated ErbB-1 variants and over-expression of ErbB-2 are frequently associated with virulent tumors, such as carcinomas and glioblastomas. Our past studies concentrated on understanding the layered structure of the ErbB network of signaling and its positive regulators, a group of adaptors and enzymes (Fig. 1). Interestingly, a significant portion of the network is devoted to tuning of signals, a process accomplished by a fine balance between positive and negative signaling pathways. Genetic evidence derived from worms and flies...
suggests that negative circuits were added to the network relatively late in evolution, and they exhibit unexpected variation and complexity. Concentrating on negative mechanisms, we found that ligand-induced endocytosis and degradation of active receptors is a major regulatory pathway involving not only phosphorylation, but also ubiquitination of receptors and associated molecules. Alongside, constitutive endocytosis and chaperone-mediated stabilization of kinase’s conformation are essential for network maintenance. In addition, because ErbB proteins are asymmetrically expressed on the surface of neuronal and epithelial cells, multi-molecular complexes regulating post-synthesis sorting are important for signaling. In-depth understanding of network’s desensitization may facilitate development of new cancer therapies. For example, antibody-induced endocytotic removal of ErbB proteins is already in clinical use and drugs interfering with kinase activity or chaperone’s function are being tested on cancer patients. Identification of still unknown mechanisms that shut down oncogenic signal transduction will eventually expand the arsenal of therapeutic strategies.

Selected Publications

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