Oncogenic signaling networks and their implications for cancer therapy

Yosef Yarden
Sara Lavi
Moshe Lindzen
Ami Citri
Menachem Katz
Ido Amit
Chanan Rubin
Yaron Mosesson
Yaara Zwang
Gabi Tarcic
Gur Pines
*Meirav Algrissy
*In collaboration with Prof. Michael Sela

Although epithelial cells constitute less than 5% of our body mass, malignant tumors of the epithelium (carcinoma) account for more than 80% of cancer mortality. Hence, mechanisms controlling growth and proliferation of epithelial cells are of high interest. We focus on a large group of growth factors, EGF and neuregulins, as well as their receptor tyrosine kinases of the ErbB family, which collectively regulate mammary, ovarian, lung and other epithelia. Point mutations and deletions within ErbB-1 (also called EGFR) have been identified in several kinds of carcinoma and brain tumors, whereas amplification of the erbB-1 and erbB-2 genes drives some head and neck and breast tumors. Due to their pivotal roles in cancer, intercepting ErbB signaling has proved beneficial in clinical settings: both anti-receptor antibodies and selective kinase inhibitors are already used in the treatment of breast, colorectal and lung cancer.

Our work has contributed to the recognition of ErbB signaling as a layered network, which shares structural and functional features with engineered information-processing systems (Fig. 1). This includes bowtie architecture, structural modularity and functional redundancy, all aimed at increasing robustness. In the last few years we have concentrated on two attributes, which are essential for the robust function of the network, namely: network buffering and system controls. This led to the identification of Hsp90 as a major buffering component that regulates the ability of ErbB-2 to form heterodimers and trans-phosphorylate other ErbBs. In addition, we proposed that by engaging in...
heterodimers, ErbB-2/HER2, a ligand-less oncogenic receptor, acts as an amplifier of ErbB signals. On the other hand, we identified an E3 ubiquitin ligase, called c-Cbl, as a major negative feedback modifier of the network. While analyzing the function of c-Cbl, we identified a cascade of E3 ligases (i.e., c-Cbl, AIP4/Nedd4 and Tal) and mono-ubiquitin-binding proteins (e.g., Hrs and Epsin) that control sorting of active receptors to vesicular trafficking and, ultimately, to intracellular degradation. Alongside, we resolved the function of several other negative feedback loops, including LRIG-1, an adhesion molecule, Ack1, an adapter that inhibits kinase activity, SOCS5, which targets ErbB-1 to proteosomal degradation, and Sprouty2, an adaptor involved in lysosomal degradation of ErbB proteins. Currently, we concentrate on tyrosine protein phosphatases and deubiquitylating enzymes that repress ErbB signaling.

A relatively new endeavor of the group comprises collaborations with Gideon Rechavi (Sheba Medical Center) and Eytan Domani (Physics of Complex Systems, WIS) that make use of DNA-arrays in order to resolve the pattern of transcription-dependent system controls. This led us to study some transcriptional regulators of the Klf family, an RNA-binding protein (Zfp36/TTP) and a cytoskeletal protein called Cten. Initial analyses of cancer patients ascribe prognostic value to some negative regulators identified using microarrays. Because many modifiers of cell motility undergo up-regulation upon ErbB stimulation, our future work will concentrate on the regulation of cell migration by the ErbB network.

Because the ErbB network is embedded in a larger network of networks, we address trans-regulation via parallel signaling pathways, including the p38 MAP kinase. This stress-activated kinase trans-phosphorylates ErbB-1, thereby enhancing receptor endocytosis following cellular stimulation by cytokines (e.g., TNF) or by chemotherapeutic agents (e.g., CDDP). This observation may relate to a well-known synergistic interaction (e.g., TNF) or by chemotherapeutic agents (e.g., CDDP). This led us to study some transcriptional regulators of the Klf family, an RNA-binding protein (Zfp36/TTP) and a cytoskeletal protein called Cten. Initial analyses of cancer patients ascribe prognostic value to some negative regulators identified using microarrays. Because many modifiers of cell motility undergo up-regulation upon ErbB stimulation, our future work will concentrate on the regulation of cell migration by the ErbB network.

Selected publications


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