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Signaling by oncogenic receptor tyrosine kinases: attenuation mechanisms and implications for cancer therapy

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Cell fate determination, as well as rapid responses to extracellular cues, are critically mediated by soluble growth factors and their transmembrane receptors. Once activated by growth factors, the receptors simultaneously launch both 'positive signals', which lead to cell stimulation, and 'negative signals', which regulate the amplitude and duration of these positive signals. A delicate balance between positive and negative signals is critical for normal cellular homeostasis, and its disturbance is often implicated in disease development. An example is provided by the ErbB family of receptor tyrosine kinases (RTKs) and their neuregulin ligands. The prevalence of positive signals, promoted by autocrine loops, overexpressed or mutated ErbB receptors, as well as unleashed downstream effectors, leads to excessive cell proliferation and is often associated with human cancer.

Unlike positive signals, which are relatively well understood, the nature and mediators of signal desensitization are only beginning to be unraveled. Our studies define two major waves of signal attenuation. The immediate phase mobilizes a group of pre-existing proteins like c-Cbl, an E3 ubiquitin ligase, and Ack-1, a cytoplasmic tyrosine kinase, which collectively sort ligand-activated receptors to the endocytic pathway. Through attachment of multiple mono-ubiquitins to the internalized receptor, the latter is successively sorted to the multi-vesicular body (MVB) and eventually to degradation in lysosomes. This endocytic pathway engages a group of ubiquitin-binding proteins (e.g., Epsin) and two additional E3 ligases, namely AIP4 and Tal, a novel MVB E3 ligase we recently identified. The second wave of signal attenuation depends on the transcription of a group of proteins, which form physical complexes with active receptors. The list includes cell adhesion molecules like LRIG-1, and adaptors (e.g., Sprouty), dual specificity phosphatases and other proteins (e.g., Mig-6/RALT). Collectively, the early and late attenuators robustly terminate signal transduction. Hence, harnessing the attenuators may be beneficial in pathologic conditions involving hyper-active signaling (e.g., psoriasis and cancer). Our studies on therapeutic monoclonal antibodies (mAbs), tyrosine kinase inhibitors (TKIs) and chaperone antagonists imply that agents which enhance receptor degradation in lysosomes (mAbs) or in proteasomes (certain TKIs and chaperone antagonists) bear therapeutic significance.

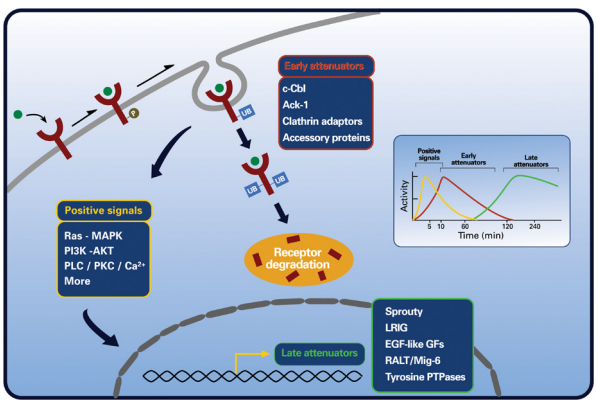

Fig. 1 *Activation-dependent mechanisms of signal attenuation. Growth factor binding to a receptor tyrosine kinase induces receptor auto-phosphorylation, followed by simultaneous activation of multiple positive signaling pathways. Cbl-mediated receptor ubiquitylation marks the onset of attenuation, starting with pre-existing molecules involved in endocytosis and cytoskeleton rearrangement (early attenuators), and culminating in transcription-dependent negative regulatory pathways (late attenuators).*

Selected Publications

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