

Receptor tyrosine kinase signaling

Extracellular signals activate transmembrane-receptor-triggered signal transduction pathways which in turn modulate the level of cell activation. For example, receptor tyrosine kinase (RTKs) initiate a cascade of events of ‘negative signaling’ that decrease the amplitude of positive signals and modulate the level of growth factor stimulation. Hence, the same receptor simultaneously induces positive and negative signals that appear to be functionally connected by numerous feedback loops. RTKs are activated by ligand binding, autophosphorylated and ubiquitinated, i.e. the small molecule ubiquitin is attached to lysine residues at various sites.

Following internalization the ubiquitinated receptor is shuttled to the endosomal/lysosomal pathway which finally terminates signaling. Negative receptor signaling involves the coordinated action of ubiquitin ligases like c-Cbl, adaptor proteins like Grb2, inhibitory molecules like Sprouty, cytoplasmatic kinases and phosphoinositol metabolites.

Fibroblast growth factor receptors (FGFR) are abundant in the nervous system and display several functions in development and during regeneration. The movie above shows a U373 glial cell transfected with FGFR1 (green fluorescence) and lysosomes in red (lysotracker). Nucleus appears blue (Hoechst stain).

Growth factor signaling and nerve regeneration

Over the recent years the cellular basis for insufficient or incorrect axonal regeneration and consequent lack of functional recovery has been unraveled in various laboratories. Neurotrophic factors such as FGFs or the neurotrophins are crucially involved in stimulating neurite outgrowth after nerve injury.

Ongoing research mainly focusses on three different aspects: 1) The molecular mechanisms of neuronal survival in response to lesion, 2) the modifications of neuronal gene and protein expression patterns required for axonal regeneration and 3) the changes in the axonal environment particularly within the distal part of the lesioned nerve.



