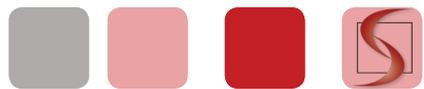


PI3K/AKT Signaling-Implications in Neuropathy and Cancer



Technical Bulletin

The PI3K (phosphoinositide 3-kinase)/AKT pathway regulates cellular size, quiescence, proliferation and longevity. Signals from various membrane receptors such as of receptor tyrosine kinases (RTKs), GPCRs and the estrogen receptor (ER) converge upon PI3K, a lipid kinase which is responsible for converting PIP₂ to PIP₃. PIP₃ promotes PDK1 translocation to the cell membrane where the protein kinase initiates AKT activation. Activated AKT directs signals to various effectors to promote cell viability. Inappropriate activation of AKT signaling can occur through several mechanisms: overexpression or increased RTK stimulation or overexpression, activating mutations in downstream kinases (such as PI3K), or alterations in PTEN, a phosphatase that targets phosphoinositide substrates including PIP₃.

Dysregulated PI3K/AKT signaling is frequently implicated in the pathogenesis of cancers and neurological disorders. In the brain, AKT activates mTOR, a protein complex that promotes the production of β -amyloid (A β) and hyper-phosphorylated Tau (p-Tau). A β and p-Tau are major components of the insoluble protein plaques and neurofibrillary tangles found in the brains of Alzheimer's disease (AD) and Parkinson's disease (PD) patients.

PI3K Activation in Cancer

PI3Ks function as heterodimers and are composed of a regulatory (p85 α , p50 α , p55 α , p85 β , and p55 γ) and a catalytic (p110 α , p110 β , p110 γ , and p110 δ) subunit. The p110 α catalytic subunit is encoded by PIK3CA and mutated versions of this gene are frequently encountered in cancers, such as breast and colorectal cancer (CRC) [1, 2]. Somatic PIK3CA mutations that activate p110 α cluster into two hotspot regions: one in exon 9, which encodes the helical domain and the other in exon 20, corresponds with the kinase domain of p110 α [3]. Almost a third of all breast cancers have PIK3CA mutations and approximately three out of four patients have amplifications of the PIK3CA gene [4, 4, 5]. PIK3CA mutations are enriched in several breast cancer subtypes, which include: estrogen receptor (ER) α -positive, progesterone receptor (PR)-positive, human epidermal growth factor 2 (HER2)/Neu-positive and triple-negative breast cancers [4]. Fortunately, primary breast cancers that have PIK3CA mutations are associated with favorable outcomes following surgical resection [4].

Approximately 15% of CRC tumors are PIK3CA mutation positive, prompting many studies into its effectiveness as a prognostic biomarker [4]. PIK3CA mutation positive individuals who take Aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs) have reduced rates of CRC recurrence and improved outlook for survival [6, 7]. However, the prognostic potential of PIK3CA mutations appears to diminish as CRC advances into later stages [8].

It is clear that PIK3CA mutations represent strong prognostic biomarkers for breast cancer, CRC and other types of malignancies. However, the PIK3CA mutations in the tumor's background also constrain the type of therapeutic options available to the patient. For example, because PIK3CA mutations activate the intracellular components of the PI3K/AKT pathway, drugs that inhibit upstream receptors such as HER2 or ER are largely ineffective [4]. This limitation is driving the development of precision therapeutics that target downstream components in the pathway, such as PI3K, AKT and mTOR.

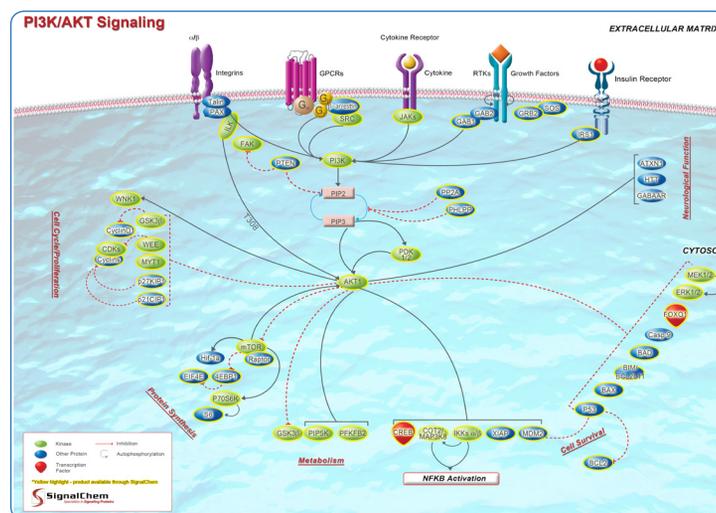


Figure: AKT-PI3K Signaling Pathway

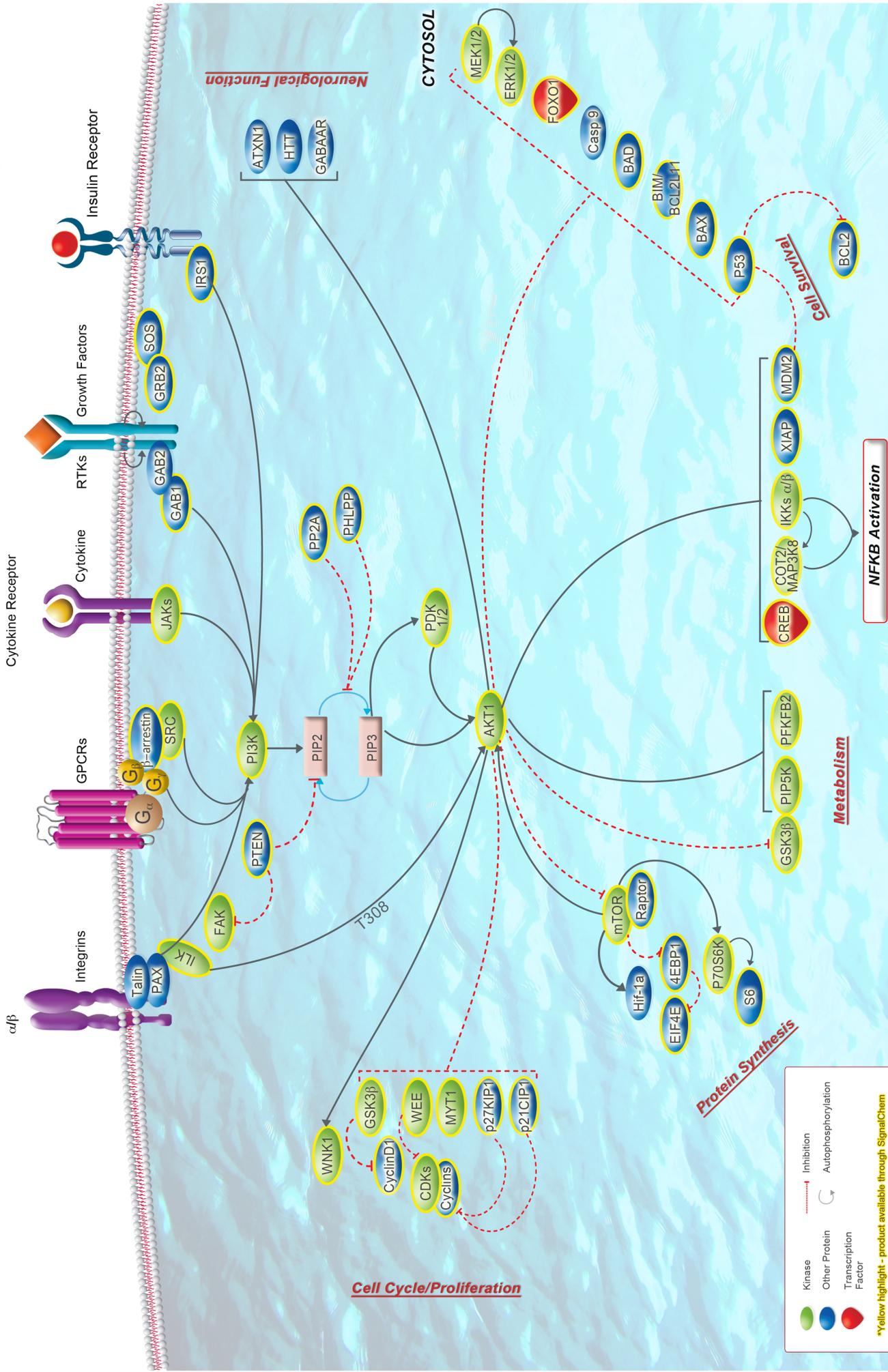
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References:

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PI3K/AKT Signaling

EXTRACELLULAR MATRIX



● Kinase
● Other Protein
● Transcription Factor
● Inhibition
● Autophosphorylation
● Factor

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