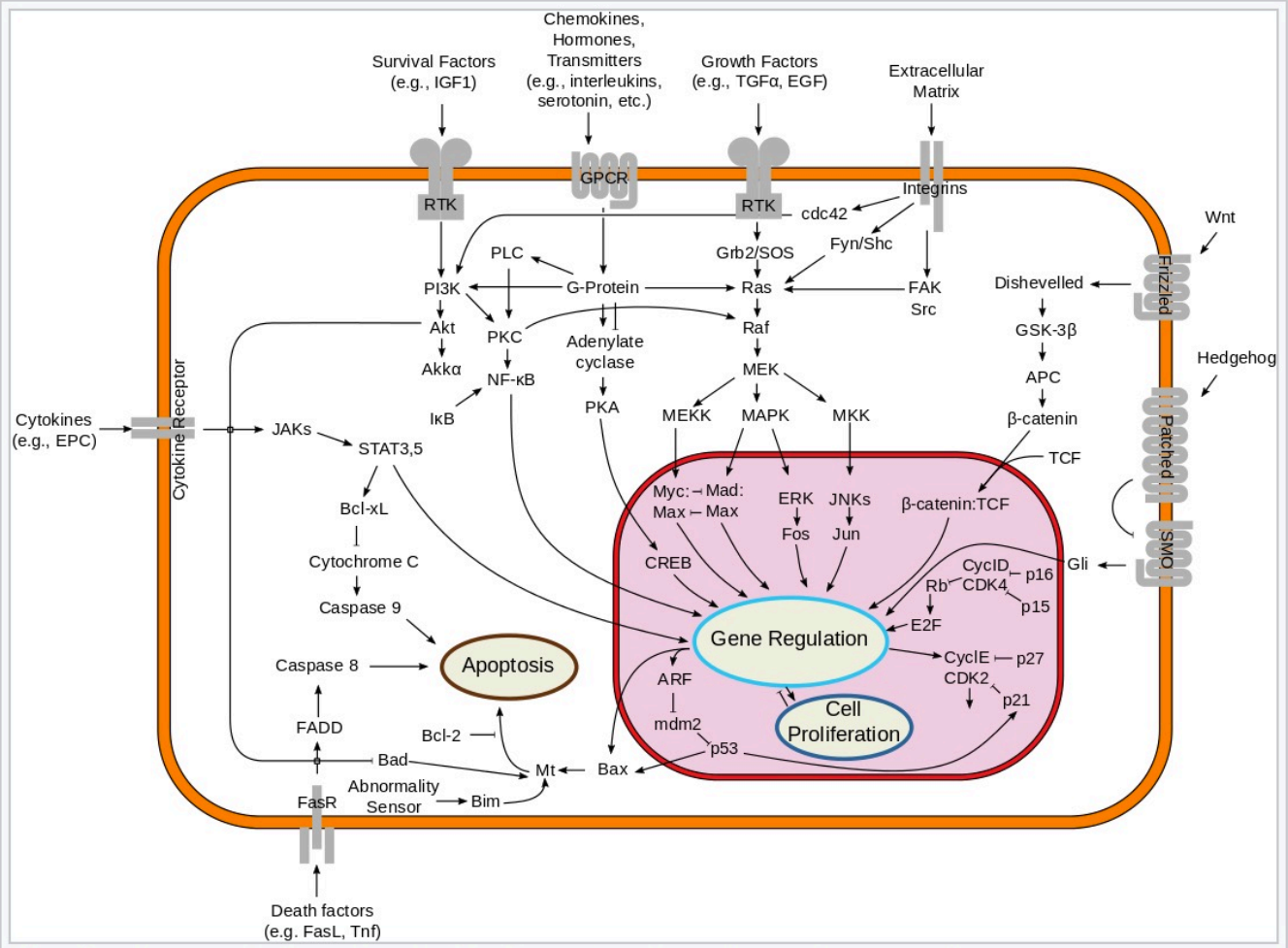
MAPK signaling pathway

Current standard treatment for glioma patients is surgical removal followed by radiotherapy and adjuvant chemotherapy. Due to therapeutic resistance and tumor recurrence, efforts are ongoing to identify the molecules that are fundamental to regulate the tumor progression and provide additional methods for individual treatment of glioma patients. By studying the initiation and maintenance of glioma, studies focused on the targets of tyrosine kinase receptors including EGFR, PDGFR and other crucial signal pathways such as PI3K/AKT and RAS/RAF/MAPK pathway. Furthermore, recent advances in targeting immunotherapy and stem cell therapy also brought numerous strategies to glioma treatment [1].



Simplified representation of major signal transduction pathways in mammals.

Activation of the MAPK pathway is well established as the oncogenic driver of the pilocytic astrocytoma. It is most frequently caused by KIAA1549:BRAF fusions, and leads to oncogene induced senescence (OIS). OIS is thought to be a major reason for growth arrest of PA cells in vitro and in vivo, preventing establishment of PA cultures [2].

Mitogen-activated protein kinases (MAPK) are protein kinases that are specific to the amino acids serine, threonine, and tyrosine. MAPKs belong to the CMGC (CDK/MAPK/GSK3/CLK) kinase group.

MAPKs are involved in directing cellular responses to a diverse array of stimuli, such as mitogens, osmotic stress, heat shock and proinflammatory cytokines. They regulate cell functions including proliferation, gene expression, differentiation, mitosis, cell survival, and apoptosis.

MAP kinases are found in eukaryotes only, but they are fairly diverse and encountered in all animals, fungi and plants, and even in an array of unicellular eukaryotes.

The closest relatives of MAPKs are the cyclin-dependent kinases (CDKs).

P38 mitogen-activated protein kinases are a class of mitogen-activated protein kinases that are responsive to stress stimuli, such as cytokines, ultraviolet irradiation, heat shock, and osmotic shock, and are involved in cell differentiation, apoptosis and autophagy.

p38 MAP Kinase (MAPK), also called RK or CSBP (Cytokinin Specific Binding Protein), is the mammalian orthologue of the yeast Hog1p MAP kinase, which participates in a signaling cascade controlling cellular responses to cytokines and stress.

Four p38 MAP kinases, p38-α (MAPK14), -β (MAPK11), -γ (MAPK12 / ERK6), and -δ (MAPK13 / SAPK4), have been identified. Similar to the SAPK/JNK pathway, p38 MAP kinase is activated by a variety of cellular stresses including osmotic shock, inflammatory cytokines, lipopolysaccharides (LPS), Ultraviolet light, and growth factors.

Suppressing p38 and extracellular signal-regulated kinase (ERK) activity affects TGF beta 1-induced analgesia during neuropathy [3].

1)
Lin L, Cai J, Jiang C. Recent advances in targeted therapy for glioma. Curr Med Chem. 2016 Dec 23. [Epub ahead of print] PubMed PMID: 28019637.
2)
Selt F, Hohloch J, Hielscher T, Sahm F, Capper D, Korshunov A, Usta D, Brabetz S, Ridinger J, Ecker J, Oehme I, Gronych J, Marquardt V, Pauck D, Bächli H, Stiles CD, von Deimling A, Remke M, Schuhmann MU, Pfister SM, Brummer T, Jones DT, Witt O, Milde T. Establishment and application of a novel patient-derived KIAA1549:BRAF-driven pediatric pilocytic astrocytoma model for preclinical drug testing. Oncotarget. 2016 Dec 17. doi: 10.18632/oncotarget.14004. [Epub ahead of print] PubMed PMID: 28002790.
3)
Chen NF, Chen WF, Sung CS, Lu CH, Chen CL, Hung HC, Feng CW, Chen CH, Tsui KH, Kuo HM, Wang HD, Wen ZH, Huang SY. Contributions of p38 and ERK to the antinociceptive effects of TGF-β1 in chronic constriction injury-induced neuropathic rats. J Headache Pain. 2016 Dec;17(1):72. Epub 2016 Aug 19. PubMed PMID: 27541934.