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SnapShot: Ras Signaling

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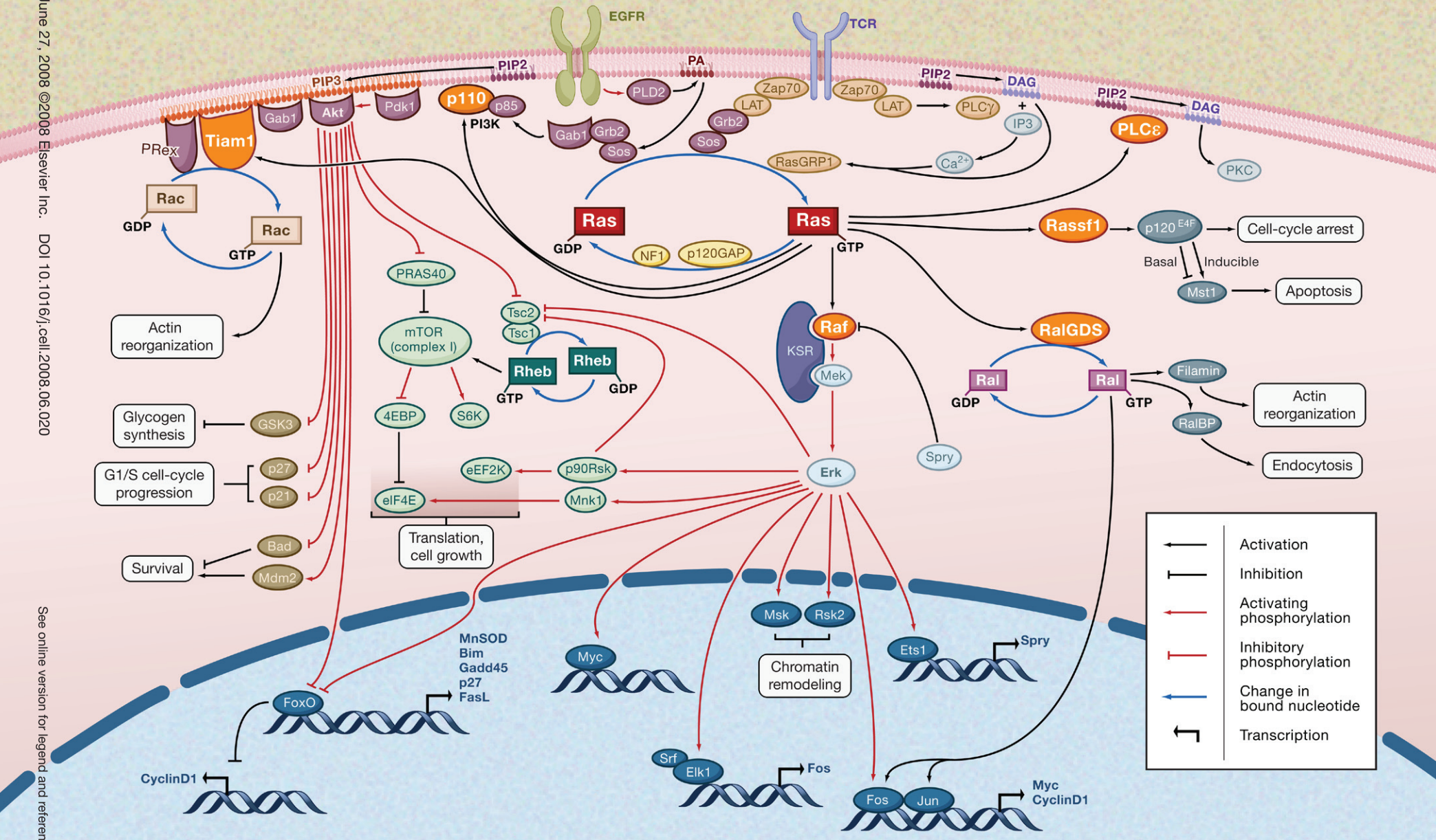
Cell



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Ras is a monomeric membrane-associated GTP-binding protein that regulates cell proliferation and survival in response to extracellular stimuli, such as activation of epidermal growth factor receptor (EGFR) or T cell receptor (TCR). Originally identified as an oncogene in murine sarcoma viruses, activating mutations in Ras have been found in about 30% of human tumors. Dysregulation of the Ras signaling pathway plays a key role in the progression of cancer. When bound to GTP, Ras is active and stimulates several downstream targets by direct interactions. Ras has intrinsic GTPase activity, which can be activated by GTPase-activating proteins (GAPs) such as the *NF1* tumor suppressor gene product and $p120^{GAP}$. Activation of Ras occurs largely through guanine nucleotide exchange factors (GEFs) such as Sos and RasGRP1, which catalyze the exchange of Ras-bound GDP with free GTP. Multiple downstream effector pathways mediate Ras signaling, including the Raf/MEK/ERK kinase cascade, the PI 3-kinase/Akt/mTor pathway, and the Ral GTPase pathway. Raf/MEK/ERK is the prototypical mitogen-activated protein kinase (MAPK) cascade, wherein each kinase phosphorylates and activates its downstream target, culminating in the activation of multiple targets including several transcription factors. Much of the recent work on the MAPK cascade has focused on negative feedback loops, such as the phosphorylation of Raf and Sos by ERK, as well as the transcription of negative regulators such as Sprouty and Spred. The second of the major downstream Ras targets, the PI 3-kinase/Akt/mTor pathway, contributes to cell growth, proliferation, and survival downstream of Ras. PI 3-kinase is a lipid kinase that phosphorylates phosphatidylinositol (4,5) bisphosphate (PIP_2) to generate the second messenger phosphatidylinositol (3,4,5) trisphosphate (PIP_3). PIP_3 activates Akt (PKB) and also GEFs for Rac GTPases, which regulate the actin cytoskeleton. Finally, Ras is able to activate another GTPase, Ral, through stimulation of the RalGDS family of guanine nucleotide exchange factors. Activation of Ral results in increased endocytosis and activation of the transcription factors Jun and Fos.

REFERENCES

Buday, L., and Downward, J. (2008). Many faces of Ras activation. Biochim. Biophys. Acta Published online March 21, 2008. 10.1016/j.bbcan.2008.05.001.

Bunney, T.D., and Katan, M. (2006). Phospholipase C epsilon: linking second messengers and small GTPases. Trends Cell Biol. *16*, 640–648.

Kolch, W. (2005). Coordinating ERK/MAPK signalling through scaffolds and inhibitors. Nat. Rev. Mol. Cell Biol. *6*, 827–837.

Malumbres, M., and Barbacid, M. (2003). RAS oncogenes: the first 30 years. Nat. Rev. Cancer *3*, 459–465.

Mason, J.M., Morrison, D.J., Basson, M.A., and Licht, J.D. (2006). Sprouty proteins: multifaceted negative-feedback regulators of receptor tyrosine kinase signaling. Trends Cell Biol. *16*, 45–54.

Mitin, N., Rossman, K.L., and Der, C.J. (2005). Signaling interplay in Ras superfamily function. Curr. Biol. *15*, R563–R574.

Mor, A., Dustin, M.L., and Philips, M.R. (2007). Small GTPases and LFA-1 reciprocally modulate adhesion and signaling. Immunol. Rev. *218*, 114–125.

Murphy, L.O., and Blenis, J. (2006). MAPK signal specificity: the right place at the right time. Trends Biochem. Sci. *31*, 268–275.

Sabatini, D.M. (2006). mTOR and cancer: insights into a complex relationship. Nat. Rev. Cancer *6*, 729–734.

Shaw, R.J., and Cantley, L.C. (2006). Ras, PI(3)K and mTOR signalling controls tumour cell growth. Nature *441*, 424–430.

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