

RAS PROTEINS AND RELATED PRODUCTS

Ras proteins act as molecular switches in the control of cellular responses to extracellular signals. They play an important role in relaying signals from receptor tyrosine kinases to the nucleus to stimulate cell proliferation and differentiation. They function as signal mediators for receptor tyrosine kinases and tyrosine-associated receptors. Ras proteins were discovered as products of mutant *ras* genes that promote cancer by altering the pathways that control cell proliferation and differentiation. Three mammalian *ras* genes (*H-ras*, *K-ras*, and *N-ras*) encode almost identical 21 kDa proteins collectively known as Ras. Activation of cell surface receptors by a signaling molecule converts Ras proteins from their inactive, GDP-bound state, to an active, GTP-bound, state. The Ras GTPase activating proteins (GAPs) preferentially associate with the GTP-bound form of Ras. GAPs accelerate the intrinsic Ras GTPase activity which inactivates Ras proteins by increasing the rate of hydrolysis of Ras-bound GTP. Most human carcinomas produce Ras proteins (oncogenic Ras proteins) that offer resistance to hydrolysis by GTPase leading to constant stimulation. This is believed to be a major factor in malignant transformation. In normal cells, Ras proteins revert to their inactive state by replacing GTP with GDP, however, mutated Ras proteins fail to perform this action which leads to an active state even in the absence of growth factors. In over 30% of human cancer, mutated Ras genes produce abnormal proteins that remain locked in an active state, leading to uncontrolled proliferative signals. The function of Ras proteins is dependent on the attachment of farnesyl group to a cysteine by the

action of protein farnesyltransferase. Several classes of FTase inhibitors have been developed that block Ras farnesylation, reverse Ras-mediated cell transformation, and inhibit the growth of tumor cells via mechanisms involving apoptosis and cell cycle regulation. These inhibitors exhibit better therapeutic index and chemotoxicity. This process imparts hydrophobicity to Ras proteins. Hence, inhibiting FTase would prevent Ras from maturing into a biologically active form. Development of selective FTase inhibitors as potential anticancer agents is of great significance. Recent interest in the development of inhibitors of farnesyltransferase has been attributed to their ability to inhibit the growth of malignant cells. CALBIOCHEM® Biochemicals offers Ras proteins and antibodies and a wide selection of inhibitors useful for signal transduction and cancer biology research.

References:

- Hao, D., and Rowinsky, E.K. 2002. *Cancer Invest.* **20**, 387.
- Shields, J.M., et al. 2000. *Trends Cell Biol.* **10**, 147.
- de Gunzburg, J. 1999. *Cell Biol. Toxicol.* **15**, 345.
- Macara, I.G., et al. 1996. *FASEB J.* **10**, 625.
- Marshall, M.S. 1995. *FASEB J.* **9**, 11311.
- McCormick, F., et al. 1994. *Trends Cell Biol.* **4**, 347.
- James, G.L., et al. 1993. *Science* **260**, 1937.
- Kahn, R.A., et al. 1992. *FASEB J.* **6**, 2512.
- Bos, J.L. 1989. *Cancer Res.* **49**, 4682.
- Barbacid, M. 1987. *Annu. Rev. Biochem.* **56**, 779.

