PERGAMON

European Journal of Cancer Vol. 38 Suppl. 5 (2002) S2

European Journal of Cancer

www.ejconline.com

Significance of tyrosine kinases in cancer: overview

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When unicellular organisms populated this planet some 2 billion years ago, growth control was not an issue. These cells were growing continuously and were restricted only by the availability of space and nutrition, and the temperature. As they grew, they divided into two new cells, and in actuality, they never got old nor did they develop cancer. With the appearance of multicellular organisms, however, the control of cell growth emerged as an important issue. Rapid cell proliferation is necessary during embryonic development, but then growth has to be turned off. When a cell loses growth control it returns to the original phenotype. It no longer obeys the rules of growth and is called cancer. Therefore, the phenotype of a cancer cell is more archaic than what is commonly defined as a "normal" cell.

The importance of communication between cells of multicellular organisms became apparent when the human genome was sequenced. Approximately 20% of all genes are involved in some way in intracellular signaling. The main switch in these signaling pathways is phosphorylation/dephosphorylation, in which a phosphate moiety is transferred enzymatically from one cellular protein to another. This reaction is analogous to a light switch, because the activity of the phosphorylated or dephosphorylated protein is either turned on or off. The phosphorylation of proteins is mediated by enzymes known as kinases, whereas the dephosphorylation reaction is mediated by phosphatases. More than 500 protein kinases and 150 phosphatases have been described.

A special class of these enzymes is the protein tyrosine kinases, which phosphorylate tyrosine residues on target proteins. Ninety tyrosine kinases are already known, and the number is expected to grow significantly. These enzymes are grouped into two classes: the transmembrane receptor tyrosine kinases that transmit information of cell surface receptors and the intracytoplasmic nonreceptor tyrosine kinases that relay intracellular signals. Together these tyrosine kinases form the largest group of dominant oncogenes.

The cells of gastrointestinal stromal tumors (GISTs) express a growth factor receptor with tyrosine kinase activity known as c-kit. The extracellular domain of c-kit receives an external signal provided by stem-cell factor and as a result it causes activation of the intracellular tyrosine kinase domain. In turn, the kinase domain relays signals intracellularly that alter gene transcription, cell proliferation, and apoptosis.

The majority of malignant GISTs express a mutated form of c-kit. Typically, the mutation is found in the juxtamembrane region, thus allowing constitutive dimerization of c-kit even in the absence of stem-cell factor. As a result, mutated c-kit provides a signal constitutively, which leads to dysregulation of cell growth. This mutation in c-kit has been implicated as a major cause of GISTs. In addition, mutations in other domains of c-kit have been described. Those occurring in the kinase domain give rise to another tumor phenotype, namely mastocytomas and mast cell leukemias.

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