MOLECULAR PATHOLOGY OF GROWTH FACTOR RECEPTORS AND KINASES IN SOLID CANCER

Fontanini Gabriella, Donati Valentina

Department of Surgery, Unit of Pathology, University of Pisa

Growth factors signals are propagated from the cell surface, through the action of transmembrane receptors, to intracellular effectors that control critical functions in human cancer cells, such as differentiation, growth, angiogenesis, and inhibition of cell death and apoptosis. Several kinases are involved in transduction pathways via sequential signalling activation. These kinases include transmembrane receptor kinases (EGFR, ERBB-2, ERBB-3, ERBB-4) and cytoplasmic kinases (PI3 kinase).

In cancer cells these signalling pathways are often altered and result in a phenotype characterized by uncontrolled growth and increased capability to invade the surrounding tissue. Therefore these crucial transduction molecules represent attractive targets for cancer therapy. The most important targeted agents currently under development interfere with function and expression of several signalling molecules, including the ERBB family; the vascular endothelial growth factor and its receptors; some cytoplasmic kinases such as Ras, PI3K and mTOR.

One of the most paradigmatic example of how kinases aberrations are crucial in the pathogenesis of human cancers and important as targets for new cancer therapy is offered by the tyrosine kinase receptors belonging to the ERBB family. The ERBB-network is a complex system characterized by interactions between its members (homo- and heterodimerization) and interfacing with other systems. The major mechanisms which lead to ERBB activation in cancer are receptor overexpression due to gene amplification or increased translation, altered ligand expression and mutations in the receptor kinase or extracellular domain. Based on these observations, ERBB-targeted inhibitors have been designed and are under development, focusing on targeting the extracellular domain of receptors with therapeutic antibodies, on blockade of the intracellular kinase domain with selective tyrosine kinase inhibitors and on drug combinations.