Growth factor signalling: ample opportunities for pharmaceutical interventions in oncology

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Growth factors are secreted proteins that mediate cell-to-cell communication. Each family of growth factors is responsible for the generation of only a few cell lineages in the developing embryo. Examples include mesenchymal growth factors, such as the platelet-derived growth factor (PDGF) family, and the endothelial growth factors (VEGFs). Another family of polypeptide growth factors, the EGF/Neuregulin family, determine cell fate in the epithelial cell lineage. Hence, the EGF/Neuregulin family is richly involved in the development of carcinomas.

Initiation of signal transduction by growth factors

Growth factors are sensed by target cells through their binding to specific receptors, collectively called receptor tyrosine kinases (RTKs) [1]. We will focus here on a prototypic subtype of RTKs, namely the ErbB family of receptors for EGF/Neuregulin peptides. The family comprises four members: ErbB-1/EGFR, ErbB-2/HER2, ErbB-3/HER3, and ErbB-4/HER4. Upon ligand binding, the extracellular domain of the receptor undergoes a remarkably large conformational change, which exposes a dimerisation loop that facilitates receptor homo- or hetero-dimer formation [2]. Within the dimer, one kinase domain activates the other in an allosteric mechanism [3]. Subsequent to ligand-induced activation, the kinase phosphorylates several tyrosine residues within the regulatory sequence of the receptor. Both cytoplasmic enzymes, whose activity is triggered by active RTKs, as well as adaptor proteins capable of forming multi-protein complexes, dock at the phosphorylated tyrosines and initiate intracellular signalling pathways.

Propagation of signal transduction by growth factors

A major signalling pathway instigated by all RTKs leads to the activation of extracellular signal-regulated kinase (Erk). Through the recruitment of the adaptor proteins Grb2 and Shc, active receptors stimulate Ras, which in turn activates Raf family protein kinases. The activated Raf then phosphorylates another protein kinase, MEK, which in turn activates Erk. Activated Erk phosphorylates various cytoplasmic and nuclear proteins including transcription factors (reviewed by Katz et al. [4]). Another major pathway participating in RTK signalling is the phosphatidylinositol-3′-kinase (PI3K) pathway. Upon activation, PI3K catalyses PtdIns(3,4,5)P_3 formation at the membrane, which serves as a docking site for the kinases PDK1 and Akt. Subsequently, PDK1 along with an unknown kinase, phosphorylates and activates Akt. Active Akt has many substrates collectively affecting diverse cellular processes, such as cell cycle progression, survival, and motility. Additionally, RTKs trigger the activation of several other signalling pathways, including Src, PLC, STAT, PKC, and JNK.

Involvement of growth factors and their receptors in cancer

The outcomes of growth factors signalling coincide with the hallmarks of tumour development [5]. Cancer-associated deregulation of growth factor signalling occurs at all steps of signal transduction (reviewed by Yarden and Sliwkowski [6]). At the input level, overexpression and autocrine secretion of ligand molecules often associate with increased growth and survival of tumour cells, leading to poorer patient prognosis. At the receptor level, activating mutations and overexpression are common mechanisms for tumour development. Focusing on the ErbB family, many studies showed correlation between EGFR and HER2 overexpression and shorter patient survival (for a recent review, see Ferretti et al. [7]). Additionally, deletions and point mutations of EGFR have been associated with malignancies: EGFRvIII, an extracellular deletion mutant, which requires no ligand for activation, is associated with glioblastomas, whereas

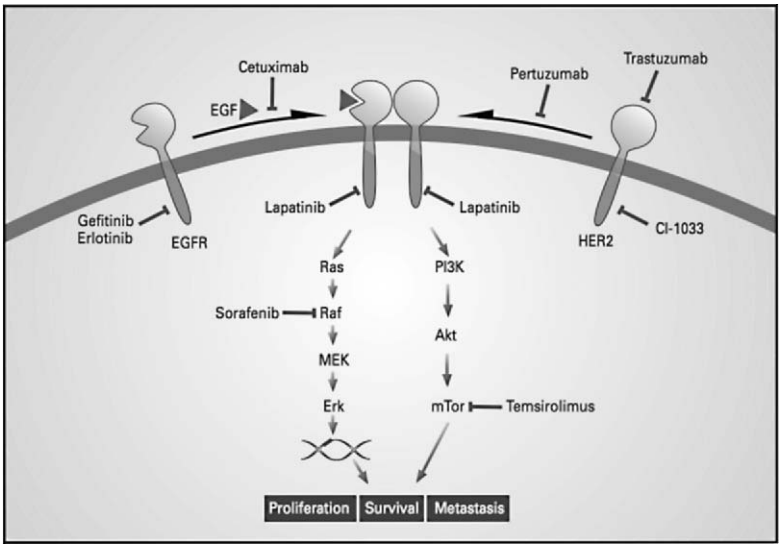

Fig. 1. Pharmaceutical interception of growth factor signalling. Signals generated by the ErbB family of RTKs may be intercepted at multiple sites. At the extracellular level, monoclonal antibodies such as Cetuximab, Pertuzumab, and Trastuzumab block receptor functions and recruit natural killer cells. At the intracellular level, small inhibitors, such as Gefitinib, Erlotinib, Lapatinib, and CI-1033, attenuate receptor's kinase activity. At the level of downstream effector molecules, inhibitors such as Sorafenib and Temsirolimus inhibit distinct signalling pathways. Note that HER2 binds no ligand growth factor and Lapatinib (as well as CI-1033) inhibits both HER2 and EGFR.

small deletions and point mutations at the kinase domain enhance catalytic activity in non-small-cell lung cancer [8]. Downstream to the receptor, activating mutations affect signalling components and associate with virulent malignancies. Examples include point mutations that lock Ras in the active GTP-bound form and loss of function mutations of PTEN, a negative regulator of PI3K activity.

Therapeutic interception of growth factor signalling (Fig. 1)

Two therapeutic anti-ErbB strategies have been successful, namely monoclonal antibodies directed at the extracellular domain of EGFR and HER2 [9], as well as small molecules that block the nucleotide-binding cleft of these receptors [10]. A well-studied drug is Cetuximab, a chimeric monoclonal antibody to EGFR. In clinical trials, Cetuximab improved patient survival, especially when combined with chemotherapy [11,12], or with radiotherapy, in the case of carcinomas of the head and neck [13]. Similarly, HER2 is targeted by Trastuzumab, an antibody that accelerates HER2 degradation and recruits natural killer cells to HER2-overexpressing breast tumours. The other therapeutic strategy aims at the tyrosine kinase domain of the receptors. Small molecule kinase inhibitors such as Gefitinib, Erlotinib, Lapatinib, and CI-1033 have been developed. For example, Erlotinib was capable of increasing the therapeutic efficacy of chemotherapies in lung cancer [14], whereas Lapatinib displayed therapeutic efficacy in breast cancer, when combined with chemotherapy [15]. More inhibitors, and especially better combinations of drugs, will likely enhance the clinical efficacy of molecular targeted therapy and likely overcome acquired resistance to novel therapies.

Conflict of interest statement

There are no conflicts of interest with this article.

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