17 Signaling by the EGF Receptor in Human Cancers: Accentuate the Positive, Eliminate the Negative

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Abstract

As described in accompanying chapters, enhanced EGF receptor (EGFR) signaling in human cancers can occur due to receptor overexpression or mutational activation. However, it may also arise from perturbations in the signal transduction pathways that function downstream of the receptor or the regulatory processes that tune the magnitude and duration of their output (Fig. 17.1). In this chapter we focus on the latter two aspects of oncogenic EGFR signaling. Specifically, we address: cancer-related changes that occur in the expression and/or activity of key signal relay molecules; pertubation of feedback control mechanisms; and attenuation of receptor down-regulation as a mechanism for signal amplification. We also discuss the impact of these changes on cellular sensitivity to EGFR-directed therapies, and how they inform more effective use of such therapies, alone or in combination with other signal transduction inhibitors, in a clinical setting.

Key Words: Src, Ras, Raf, Erk, PI3-kinase, PTEN, feedback loops, c-Cbl, endocytosis, EGFR inhibitors.

1. ONCOGENIC CHANGES IN SIGNAL TRANSDUCERS

Ligand binding to the EGFR promotes receptor dimerization and kinase activation, leading to autophosphorylation of particular tyrosine residues within its cytoplasmic domain (*1, 2*). These phosphorylated residues provide binding sites for specific src homology (SH)2 and

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