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Biochemistry, Epidermal Growth Factor Receptor

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Introduction

Epidermal growth factor receptor (EGFR), also known as ERBB, ERBB1, HER1, NISBD2, PIG61, and mENA, is a transmembrane glycoprotein with an intracellular tyrosine kinase that serves as a receptor for extracellular protein ligands. EGFR was the first member of the ErbB receptor family to be described. The ErbB receptors are a subfamily of four tyrosine kinase receptors including EGFR, HER-2/neu, HER-3, and HER-4. Ten different ligands can selectively bind to each receptor, and ligand binding leads to downstream pathways involved in cellular growth and proliferation as well as differentiation.

EGFR overexpression is involved in multiple tumors and is associated with neurodegenerative diseases such as Alzheimer disease. The pathologies associated with EGFRs have led to novel treatment modalities, including monoclonal antibodies designed to inhibit EGFR signaling.

Fundamentals

EGFR was the first discovered epidermal growth factor receptor. Growth factor binding results in receptor dimerization, subsequent tyrosine kinase activity and autophosphorylation of specific tyrosine residues including Y992, Y1045, Y1068, Y1148, and Y1173. Eventual downstream activation of signal transduction cascades, including MAPK, Akt and JNK pathways, leads to DNA synthesis, cell proliferation, and differentiation.

In considering EGFR, also known as ErbB-1, it is important to also consider the three related receptors of the ErbB family: ErbB-2, ErbB-3, and ErbB-4. ErbB-2 is also known as HER2 in humans and neu in rodents. In humans, the HER2 oncogene is associated with breast cancer and has become a target of therapy for associated breast cancers. ErbB-3 binds to heregulin and NRG-2. The function of ErbB-3 is yet unknown. ErbB-3 homodimers are non-functional; consequently, ErbB-3 is thought to be an allosteric activator of the other ErbB receptors. Finally, ErbB-4 binding results in mitogenesis and differentiation. Single-nucleotide polymorphisms of ErbB-4 have been implicated in amyotrophic lateral sclerosis type 19.

Function

EGFR binding by various ligands, including epidermal growth factor (EGF) and tumor growth factor-alpha (TGF-a), results in routine cellular processes such as proliferation, differentiation, and cellular development.

EGFR is a 170 kDalton single polypeptide chain of 1186 amino acids expressed on the majority of human cells. This receptor is made up of an extracellular, intracellular and transmembrane region. The extracellular region facilitates ligand binding. Binding ligands include EGF, heparin-binding EGF-like growth factor (HB-EGF), TGF-a, amphiregulin, epiregulin, betacellulin, and epigen. These ligands share a conserved motif of six cysteines. The intracellular carboxy-terminal region is a tyrosine kinase. This tyrosine kinase autophosphorylates specific intracellular tyrosine residues, with Tyr-1173 serving as the major autophosphorylation site. The transmembrane region is a single hydrophobic anchor which traverses the cell membrane.

EGFR binding and activation results in many downstream processes. The EGFR tyrosine kinase domain activates Ras, which eventually leads to DNA synthesis and cell proliferation. The MAP kinase pathway is also activated through EGFR binding of Grb-2, with subsequent recruitment of the Ras GDP/GTP exchange factor Sos, for intracellular binding to the activated EGFR. EGFR tyrosine kinase activity also influences the progression of cells from G1 to S phase. While the specific functions of EGFR activity are still a subject of scientific research, the general function of EGFR is indicated to be cellular growth, proliferation, and differentiation. As a specific example, EGFR agonism with amphiregulin and other ligands has been shown to induce ductal and lobuloalveolar development, demonstrating its effects on proliferation of mammary glands and ductal development.

Mechanism

EGFR signaling commences with ligand binding. Ligand binding to the extracellular region of the receptor results in dimerization of the receptors. Homodimerization of EGFR receptors, in addition to heterodimerization of the EGFR with any of the other ErbB receptors, results in activation. It is important to note that homodimerization of the ErbB3 receptor does not result in this same active configuration, and ErbB3 receptors are only active after heterodimerization with an alternate ErbB receptor, such as EGFR.

After ligand binding and dimerization, autophosphorylation of specific intracellular tyrosine kinase residues induces formation that allows binding sites for signal transduction substrates. Substrates include phospholipase C-gamma 1 (PLC-gamma1), GTPase-activating protein (GAP) and the syp phosphotyrosine phosphatase. The tyrosine kinase domain can also bind adapter proteins such as the srs homology and collagen (Shc) protein and Grb-2. Altering all of the specific tyrosine kinase autophosphorylation sites results in significantly decreased substrate binding. However, altering only one of the sites can be compensated by binding to the others. Substrate binding leads to downstream signaling, facilitating cell growth and proliferation.

Inactivation of the EGFR is achieved by internalization of the receptor with subsequent lysosomal degradation. Internalization is dependent on tyrosine kinase activity, and activated receptors are internalized. Additional inactivation can be achieved by phosphorylation of serine and threonine residues in the cytoplasmic domain, with subsequent receptor desensitization and reduction of downstream signaling.

Pathophysiology

EGFR has demonstrated expression on vascular endothelial cells, HeLa cells, conjunctiva cells, vascular and uterine smooth muscle cells, keratinocytes, amniotic cells, placental membranes, HeLa cells and normal skin fibroblasts. It is no surprise that many cancers have been associated with upregulation of EGFR and overexpression has been identified in the majority of solid tumors. Associated cancers include breast, head-and-neck, non-small-cell lung and squamous cell lung cancers, renal cell, ovarian, colon, bladder, pancreatic cancer, and gliomas. While normal cells express 40,000 to 100,000 EGFR receptors, cancer cells may express up to 2,000,000 receptors. Stimulation of overexpressed EGFR receptors may contribute to the pathology of cancer by inducing cancer-cell proliferation while simultaneously blocking apoptosis, by activating invasion and metastasis of hyperproliferative cells and by stimulating tumor-induced neovascularization. The degree of overexpression correlates with tumor progression, resistance to chemotherapy and a poor prognosis. In addition to their role in cancer cells, EGFR overexpression has been implicated in neurodegenerative diseases. In Alzheimer disease, mutations in presenilin 1 (PS1) contribute to the pathophysiology of the disease. PS1 is also involved in the transportation and production of EGFR. Neurites in proximity to the neuritic plaques found in Alzheimer disease show strong EGFR immunoreactivity and excess EGF is known to induce neuronal death. Although the precise mechanism of this relationship is unclear, recent research indicates that there is a role for EGFR overexpression in neurodegenerative disease as well.

Clinical Significance

Given the involvement of EGFR in the pathology of cancers, EGFR inhibitors have been considered as potential therapeutic agents for cancer. Currently, 2 mechanisms of inhibition are used to inhibit EGFR:

- Anti-EGFR monoclonal antibodies
    - Anti-EGFR monoclonal antibodies (cetuximab, panitumumab, erlotinib, and gefitinib) act as competitive inhibitors of EGFR ligand binding
- EGFR tyrosine kinase inhibitors
    - EGFR tyrosine kinase inhibitors (gefitinib, erlotinib, brigatinib, lapatinib) are small molecules that bind and inhibit the EGFR intracellular tyrosine kinase, which prevents further downstream activation

These therapies have been approved for treatment of some cancers, including lung cancer and colon cancer. A side effect of both classes of medications is a papulopustular eruption, seen in 90% of patients.

Although these treatments are promising, resistance is often seen. The T790M Mutation and MET oncogene are the 2 primary sources of resistance.

Questions

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