

Review Article

Receptor tyrosine kinase signaling pathways: a review

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Received: 02 August 2016

Revised: 20 August 2016

Accepted: 06 September 2016

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ABSTRACT

The two important enabling characteristics of cancer cells are uncontrolled proliferation and loss of programmed cell death (enhanced survival). These processes are tightly controlled by the discrete integration of signalling cascades that translate extracellular and intracellular cues into specific output responses. Alterations in these pathways in cancer cells by mutation, amplification/deletion, chromosomal translocation, over expression, or epigenetic silencing lead to constitutive activation or suppression of signalling. We will review the major signal transduction cascade well known as the receptor tyrosine kinase pathway, focussing on their common alterations in human cancers and their clinical implications and therapeutics. Since major drug development efforts are presently being focused on the development of targeted inhibitors of oncogene-activated signalling pathways, a detailed understanding of these normal physiological pathways along with their deregulation in cancer will be required of both basic cancer researchers and practicing clinical oncologists for betterment of mankind suffering. Hence with this requirement in mind we have written this article to highlight some of the most important signal transduction pathways that is receptor tyrosine signalling pathways.

Keywords: EGFR, PDGFR, Receptor tyrosine kinase pathways

INTRODUCTION

The two important enabling characteristics of cancer cells are uncontrolled proliferation and loss of programmed cell death (enhanced survival). These processes are tightly controlled by the discrete integration of signaling cascades that translate extracellular and intracellular cues into specific output responses. The signaling pathways are often initiated on binding of ligand to the extracellular domain of a receptor. This is followed by recruitment of adaptor proteins or kinases that activate an intracellular cascading network of protein and lipid intermediaries producing a cellular response. Alterations in these pathways in cancer cells by mutation, amplification/deletion, chromosomal translocation, over expression, or

epigenetic silencing lead to constitutive activation or suppression of signaling. We will review the major signal transduction cascade well known as the receptor tyrosine kinase pathway, focussing on their common alterations in human cancers and their clinical implications and therapeutics.

Receptor tyrosine kinase signaling

Receptor tyrosine kinases (RTK) include a family of transmembrane cell surface receptors that transduce extracellular signals internally in to the cell. These play a role in cell growth, survival and/or cellular phenotypes.^{1,2} Growth factors bind to the extracellular ligand binding domain of RTKs and induce dimerization of two receptor

monomers, juxtaposing the intracellular tyrosine kinase domains of each monomer.^{3,4} This dimerization results in transphosphorylation of tyrosine residues within the cytoplasmic domains. They recruit a variety of intracellular proteins through Src homology 2 (SH2) domains.⁵ Each domain is part of a larger adaptor protein. Recruitment of signaling intermediaries to the plasma membrane facilitates their interaction with membrane-bound proteins responsible for stimulating a diverse array of downstream pathways. Approximately 20 classes of RTKs have been defined based on growth factor specificity.

Epidermal growth factor receptor signaling

In 1978, the epidermal growth factor receptor (EGFR) was identified as the cell surface binding site for EGF.⁶ Subsequently tyrosine phosphorylation was identified, which had potential implication in oncogenesis.^{7,8} The amino acid sequence of EGFR was homologous to the avian erythroblastosis virus erbB oncogene, which potentially induces erythroleukemia.^{9,10} The EGFR class of RTKs comprises four receptor proteins encoded by four genes: EGFR (ERBB1), HER2/neu (ERBB2), HER3 (ERBB3), and HER4 (ERBB4). Clinically important EGFR ligands include EGF, transforming growth factor (TGF)- α and heparin-binding (HB)-EGF among many others.^{11,12} However specific ligand for HER2 has not yet been identified. HER2 is activated through heterodimer formation with other ligand-bound receptors preferably with EGFR.¹³ These heterodimers are more stable than EGFR homo dimers. They have a longer duration of action, a lower rate of endocytosis which slows dissociation of EGF from EGFR along with increased recycling to the cell surface.¹⁴⁻¹⁶

HER2-HER3 hetero dimers possess the most potent mitogenic activity among the other combinations.¹⁷ HER3 does not have intrinsic kinase activity and preferentially forms hetero dimers with HER2.¹⁸

EGFR mutations are found in 10% to 50% of non-small cell lung cancers. 80% of these are Kinase domain deletions (exon 19) and mutations (exon 21).^{19,20} Overexpression of wild-type EGFR due to gene amplification is seen in non-small cell lung, breast, gastric, colorectal, and head and neck cancers.^{21,22} HER over expression is seen in 30% of breast cancers.²³ In glioblastoma multiforme, the extracellular domain of EGFR is deleted expressing a constitutively activated truncated mutant protein (EGFRvIII).^{24,25}

Targeted agents include gefitinib and erlotinib, both of which are used for the treatment of non-small cell lung cancers that harbor activating EGFR kinase mutations.²⁶ Cetuximab, binds to the extracellular domain of EGFR and competitively inhibits ligand binding, is approved for the treatment of colorectal and head and neck cancers.²⁷⁻²⁹ Trastuzumab binds to the extracellular domain of HER2 is used in the treatment of breast cancers that display

HER2 overexpression. Pertuzumab binds to the dimerization domain resulting in impaired dimer formation.³⁰ Lapatinib is used in combination with capecitabine in HER2-overexpressing advanced or metastatic breast cancer who have progressed on trastuzumab and certain classes of chemotherapy.³¹

Mechanisms of resistance include overexpression of other HER kinase family members and/or ligands, phosphatase and tensin homolog (PTEN) loss, and the expression of a truncated HER2 protein lacking the extracellular antibody binding site.³² Addition of trastuzumab to chemotherapy compared with chemotherapy alone is associated with improved overall survival in patients with HER2-overexpressing esophagogastric cancer.³³

Insulin and insulin-like growth factor-1 receptor signaling

The insulin receptor exists as two isoforms.³⁴ The IGF1 receptor (IGF1R) can dimerize with either of the insulin receptor isoforms or with itself. The insulin receptor is stimulated by insulin or insulin-like growth factor-2 (IGF2), whereas IGF1R can be activated by either IGF1 or IGF2.^{35,36} After ligand binding, IGF1R dimerizes and undergoes transphosphorylation, leading to activation of downstream RAS-RAF-mitogen-activated protein kinase (MAPK) and the PI3K-AKT-mammalian target of rapamycin (mTOR) cascades.³⁷

Amplification of the IGF1R gene locus has been identified in colon, pancreatic, and lung cancers. Sarcomas often have either increased expression of the IGF1 and IGF2 ligands or decreased insulin-like growth factor binding protein-3 expression (Ewing sarcoma), which results in increased IGF1 levels in the tumor microenvironment.³⁸ Gastrointestinal stromal tumors (GISTs) lacking KIT and platelet-derived growth factor receptor (PDGFR) mutations also commonly harbor IGF1R amplification.³⁹ IGF1R overexpression has also been observed in up to 44% of breast tumors and may mediate resistance to HER2-directed therapies.⁴⁰

The insulin receptor family members anaplastic lymphoma kinase (ALK) and ROS1 were also recently implicated in tumorigenesis.^{41,42} In NSCLC, there is expression of an EML4- ALK fusion protein in 2% to 5% of patients.⁴³ Who often exhibit dramatic radiographic responses to crizotinib, an inhibitor of the ALK, ROS1, and MET tyrosine kinases.⁴⁴ EML-ALK fusions are found in a mutually exclusive pattern with EGFR kinase domain mutations.^{45,46}

Platelet-derived growth factor receptor signaling

PDGF signaling implicated in organ development, including lung, intestinal epithelial folding and glomerular capillary tuft formation. They also promote angiogenesis, wound healing, and erythropoiesis.⁴⁷ Four isoforms of PDGF have been identified: PDGF-A, -B, -C,

and -D.⁴⁸ Its receptor subtype PDGFR- α inhibit chemotaxis, whereas PDGFR- β stimulate chemotaxis within fibroblasts and smooth muscle cells.⁴⁹

Excess autocrine secretion of PDGF is noted in glioblastoma and sarcomas, while gain-of-function mutations that cause constitutive tyrosine kinase activation are seen in gastrointestinal stromal tumors.⁵⁰ Translocation of either the PDGF or PDGFR genes are found in dermatofibrosarcoma protuberans, chronic myelomonocytic leukemia, and hypereosinophilic syndrome) and PDGFR gene amplification are seen in glioblastoma.⁵¹⁻⁵⁴ PDGFR- α mutations are found in about 10% of KIT wild-type GISTs. The D842V mutation seen in about two thirds of PDGFR- α activating mutation is resistant to inhibition by imatinib. Dermatofibrosarcoma protuberans shows overexpression of PDGF- β and subsequent stimulation of PDGFR signaling.

Imatinib is also approved for use in patients with KIT mutant GISTs and Philadelphia chromosome-positive hematologic cancers.⁵⁵ The KIT RTK is a member of the type III RTK family that includes PDGFR and Fms-like tyrosine kinase-3 (FLT3).^{56,57} Stem cell factor (SCF) is the ligand for KIT.⁵⁸⁻⁶¹ Hot-spot mutations in exons 9 and 11 of KIT have been identified in GISTs and melanomas.⁶²⁻⁶⁵

The FLT3 receptor, a member of the RTK class is involved in the development of normal hematopoietic cells. Internal tandem duplication within exons 14 and 15 of the FLT3 gene is found in one third of acute myelogenous leukemias (AMLs) associated with a poor prognosis.⁶⁶

Fibroblast growth factor receptor signaling

Fibroblast growth factors (FGFs) bind to the extracellular domain of the FGFRs inducing FGFR dimerization and transphosphorylation of intracellular tyrosine residues and activation of multiple downstream signaling proteins in the same manner as previously described for other RTKs. Unique to the FGFR signaling complex is FGFR substrate 2 (FRS2), an adaptor protein that binds to specific phosphotyrosines on the intracellular domain also serving as a docking site for the Grb2-Sos adaptor complex which finally activates the RAS/RAF/MAPK pathway. It also activates PI3K/AKT/MTOR pathway by a different site specific interaction on docking protein.

Activating mutations within FGFR3 occur in up to 70% of non-muscle invasive bladder cancers and in 15% of patients with advanced urothelial tumors.^{66,67} FGFR3 mutations are commonly located within the extracellular domain and promote ligand-independent receptor dimerization through formation of an aberrant disulfide bridge between two receptor monomers stabilizing and activating the downstream complex.⁶⁸ Up to 15% of multiple myelomas harbor an intergenic 4;14 translocation between the FGFR3 gene and the

immunoglobulin heavy chain locus. Approximately 10% of diffuse-type gastric cancers display FGFR2 gene amplification.^{69,70} Autocrine and paracrine FGF ligand secretion has been reported to occur in a subset of melanomas and prostate cancers, respectively.^{71,72}

The close structural similarity between these RTKs has made development of FGFR selective inhibitors challenging. To date, anti-FGFR antibodies have not entered clinical testing, although preclinical studies have shown promising antitumor effects in urothelial cancer (both FGFR3 wild-type and mutant) and t(4;14) expressing multiple myeloma cell lines.⁷³

RET signaling

The RET (rearranged during transfection) protein is a RTK important for the normal development of the kidney and the enteric nervous system.^{74,75} RET is expressed predominantly on the surface of neural crest tissues, and glial-derived neurotrophic factors (GDNFs) serve as its ligands. Intracellular tyrosine residue specificity has sub functions like serving as a docking site for the STAT3 transcription factor, activation of focal adhesion kinase promoting cell migration and metastatic spread. Additional pathways diverging are MAPK, PI3K/AKT, and phospholipase C- γ pathways which promote cellular proliferation and survival.⁷⁶

Germline RET mutations are the basis for the multiple endocrine neoplasia type 2 syndromes who are noted to develop familial medullary thyroid carcinomas.⁷⁷ Sporadic medullary thyroid carcinomas are much more common, and up to 60% of such tumors harbor somatic mutations in RET. Vandetanib, an oral inhibitor of RET, EGFR, and VEGFR, was recently approved by the FDA for the treatment of patients with advanced medullary thyroid cancer.⁷⁸ Cabozantinib, an oral, multitargeted TKI that inhibits RET, VEGFR2, and MET is being evaluated in unresectable, locally advanced, or metastatic medullary thyroid carcinoma.⁷⁹

Vascular endothelial growth factor signaling

Six vascular endothelial growth factor (VEGF) ligands have been identified, VEGF-A, -B, -C, and -D, along with placental growth factor 1 and 2.⁸⁰ VEGF-A enhances vascular permeability and stimulates endothelial cell proliferation, resulting in new blood vessel formation. VEGFRs are receptor tyrosine kinases that possess an extracellular domain with seven immunoglobulin-like regions, a transmembrane domain, and an intracellular tyrosine kinase domain. VEGF-A, VEGF-B, and placental growth factor all bind VEGFR1, but the exact role of VEGFR1 in tumor angiogenesis has yet to be fully elucidated. Evidence shows that it can act as a decoy receptor that prevents ligand-mediated stimulation of VEGFR2. VEGFR2 is considered the primary receptor through which VEGF exerts its angiogenic effects.⁸¹

Bevacizumab, by binding to free VEGF and blocking its association with VEGFR, has been approved in combination with chemotherapy in metastatic colorectal and nonsquamous NSCLCs.^{82,83} It has also clinically documented activity in glioblastoma and metastatic renal cell carcinoma.^{84,85} Sorafenib and sunitinib are multitargeted TKIs with nanomolar potency for VEGFR2. Sunitinib is used in the treatment of metastatic renal cell carcinoma, GISTs, and pancreatic neuroendocrine tumors.⁸⁶ Sorafenib has been approved for the treatment of liver and renal cell cancers.^{87,88} Pazopanib is approved for the initial treatment of metastatic renal cell carcinoma and in cytokine-pretreated patients, while axitinib is approved in the second-line setting after failure of prior systemic therapy.^{89,90}

Resistance mechanisms include the activation of redundant signaling pathways that promote angiogenesis, the recruitment by tumors of bone marrow derived endothelial progenitor cells, increased pericyte density around existing blood vessels that enhances vascular growth and survival, and the ability of tumor cells to invade surrounding stroma to co-opt additional blood supply.⁹¹

Hepatocyte growth factor receptor signaling

The hepatocyte growth factor receptor (HGFR or MET) is encoded by the MET gene.⁹² Upon binding of hepatocyte growth factor (HGF) to the extracellular portion of MET, receptor dimerization occurs, followed by transphosphorylation. Adaptor proteins like GRB2 and GAB1 promotes the activation of the MAPK and PI3K/AKT signaling pathways.⁹³ MET can also activate CDC42 and p21-activated kinase, concerned with regulation of cytoskeletal proteins, integrin expression and activation finally controlling cell migration.

EGFR activation can stimulate MET signaling, and resistance to EGFR inhibitors in some lung cancers is known to occur due to MET gene amplification.⁹⁴ Germline mutations of MET are found in hereditary papillary renal cell carcinomas. MET overexpression is observed in sporadic papillary cancers, as well as collecting duct carcinomas.⁹⁵ MET amplification is associated with a worse prognosis in lung and gastric cancers, and expression of MET and HGF are unfavorable prognostic biomarkers in liver, kidney, colorectal, and gastric cancers.⁹⁶ Studies suggest an improvement in progression-free survival with the addition of anti-MET antibodies to an EGFR inhibitor in patients whose tumors display MET overexpression.⁹⁷

CONCLUSION

We know that mutational and epigenetic alterations induce constitutive activation of a wide array of signaling pathways in human tumors. Since major drug development efforts are presently being focused on the development of targeted inhibitors of oncogene-activated

signaling pathways, a detailed understanding of these normal physiological pathways along with their dysregulation in cancer will be required of both basic cancer researchers and practicing clinical oncologists for betterment of mankind suffering. Hence with this requirement in mind we have written this article to highlight some of the most important signal transduction pathways i.e. receptor tyrosine signaling pathways.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

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Cite this article as: Pathi N, Viswanath S, Pathak A, Rathore A, Prukayastha A. Receptor tyrosine kinase signaling pathways: a review. *Int J Adv Med* 2016;3:783-9.