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Role of Tyrosine Kinase Receptors in Growth Factor Mediated Signal Transduction, with Specific Reference to MAPK/Rasand p13k-Akt Containing Pathways in Oncogenesis: A Qualitative Database Review

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Abstract

Receptor Tyrosine kinases (RTKs) play a crucial role in the signal transduction pathways at cellular levels. RTK plays a vital role in cellular communication and transmission of signals to the adjacent cells and regulates different functions of the cell, such as cellular growth, differentiation, metabolism and motility. RTK s triggers growth factor receptors such as epidermal growth factor, insulin growth factor-1 receptor, platelet derived growth factor receptor, and fibro blast growth factor receptor and vascular endothelial growth factor receptor, thereby initiating and regulating cell growth and proliferation. MAPK/RAS and PI3/AKT pathways are the major pathways of RTK's function. Dysregulation of these RTK's and pathways often leads to many diseases such as Noonan Syndrome, Logius Syndrome, CFC syndrome and different types of cancer. Point mutation and over expression of receptors and mutations in Ras leads to 30% of human cancers. Also over expression of different growth factor receptors by RTK too lead to several types of cancers as Glioblastoma, Thyroid cancer, Colon cancer and Non-small cell lung cancer. PTEN mutation in PI3/AKT pathway often leads to carcinoma relative to Thyroid, Skin, Large intestine, eye and Bone. Therefore, these RTK's often used as targets for cancer therapies. The medical sector uses various types of small molecule tyrosine kinase inhibitors such as ATP competitive inhibitors, Allosteric inhibitors and covalent inhibitors which are known as Afatinib, Crizotinib, Eroltinib, Icotinib, Lepatinib and Lenvatinib in treatment and management of differential carcinomas.

Keywords

Receptor Tyrosine Kinase, PI3/AKT, MAP Kinase, PTEN, Cancer, Receptor Inhibitor

1. Introduction

Receptor tyrosine kinases (RTKs) belong to the enzyme coupled receptor family. These are vital components of Growth factor mediated signal transduction pathways [1]. These RTKs are transmembrane proteins usually monomers that hold 90 human genomic kinases. Out of them, 58 is receptor types belong to 20 sub families. The rest of the 32 are non-receptor types of 10 subfamilies [2].

During homeostasis and embryonic development, RTKs are mostly active. This also regulates cell growth, division, cell survival and cellular metabolism [3]. Domains and ligands of RTKs are illustrated in **Table 1** respectively.

Table 1. Growth factors of RTK [4].

Class	Receptor	Structure	Factor	Target
I	Epidermal growth factor receptor (EGFR)	Rich in cysteine nitrogenbase	Epidermal growth factor (EGF)	Mesenchymal and epidermalcells
II	Insulin growth factor-1 receptor (IGF-1 R)	Hetero tetramers rich in cysteine	Insulin growth factor (IGF)	Hepatocytes, muscles and other cells
III	Platelet derived growth factor receptor (PDGFR)	Has a kinase insert and 3 immunoglobulin domains	Platelet derived growth factor (PDGF)	Mesenchymal and trophoblast
IV	Fibro blast Growth factor receptor (FGFR)	Contain acidic domain, kinase insert and 3 immunoglobulins like domain	Fibro blast growth factor (FBF)	Mesenchymal, fibroblast and other cells
V	vascular endothelial growth factor (VEGF) receptor	contains kinase insert domain and 7 immunoglobulins	vascular endothelial growth factor (VEGF)	Endothelial and mesenchymal cells

2. Receptor Tyrosine Kinase Pathway

2.1. MAP Kinase Pathway

First, the mitogen activated protein kinase signaling pathway (MAPK) begins with the binding of ligand, for example, EGF to the ligand binding domain of RTK. This binding leads to the dimerization and auto phosphorylation of RTK and two sub-units present on the inner side of RTK [5]. Subsequently, the growth factor receptor bound protein-2 (GRB-2) along with SH2 domain binds to the phosphorylated RTK whereas SOS binds to GRB-2. Inactive RAS bound to GDP nucleotide becomes active after binding to SOS. SOS catalyzes GDP against GTP [6]. This activation of RAS protein could bind to several effector proteins such as B-Raf. This activated B-Raf phosphorylates and activates MEK 1/2 which in turn phosphorylates and activates ERK 1/2. Finally, it leads to the activation of transcription factors that belong to the activator protein-1 family (AP-1). Jun and Fos are the key players in AP-1 family. Activated Jun and Fos forms heterodimer which activates AP-1 motive of the DNA. Eventually leading to the expression and encoding of many genes for example cyclins, growth factors and cytokines. As a direct consequence cell proliferation is activated. This pathway is regulated through GTPase activating protein (GAP). GAP hydrolyses the GTP which is bound to RAS to GDP and inactivates the pathway [7].

2.2. PI3-AKT Pathway

The binding of one of the ligand EGF to the ligand binding domain of RTK leads to the activation of PI3-AKT pathway. This binding also auto phosphorylates the RTK which activates PI3 kinase. Activated PI3 kinase adhere and phosphorylates PIP2 which is a standard constituent of the cell membrane to PIP3. This PIP3 thereby activates serine, threonine kinases (AKT) pathway which promotes cellular growth, proliferation, glucose metabolism and inactivates apoptosis. This pathway is controlled by a regulator called Protein tyrosine phosphate (PTEN) which can change the activated PIP3 to PIP2 [8].

3. Role of the Pathways to Promote Cell Survival and Proliferation Which if Unchecked Can Be Pathogenic

In normal cells, MAPK/RAS and PI3/AKT pathways lead to cell growth and proliferation via initiating transcription factors (AP-2, Elk, CREB) and also protein synthesis. Whereas in a cell cycle Go and G1 phases play a vital role. However, these phases depend on ERK 1/2 signal transduction [9]. These pathways are regulated by RAS, growth factor receptors and non-receptor kinases. Also regulates protein translations via MEK, ERK, P20RSK, P70S6K, MNK1-2, rps6, Elf4-(A,B,E,G) and PABP. MAPK/RAS pathway also promotes post-transcriptional modification and apoptosis through PTEN and FOXO. This also phosphorylates BIM, BAX, BAD proteins which inhibit apoptosis through BCl-2, Ask and MCl-2 [10].

In addition to cell proliferation and protein synthesis through phosphorylation of mTOR, PI3/AKT pathway regulates CDK inhibitors which promote the cell cycle and inhibits caspase 9, FKHR and BAD which promote apoptosis. This also phosphorylates BIM, BAX, BAD proteins which inhibit apoptosis through Foxo-3 and β-catenin [11].

Scientific literature show cases that mutations in Ras, Raf, PIK3CA, PTEN, AKT, TSC-1, TSC-2, P38 and JNK which belongs to the above said two pathways along with the upstream regulation of receptors leads to the constant activation of these pathways. Eventually leading to neurological diseases, cancers, premature aging and diabetes. These mutations lead to a phenomenon called gene amplification. In turn results in excessive transcription and production of receptors gradually leads to overexpression of receptors on tumor cells' surface which triggers the growth phase by binding of ligands and structural change of receptors continuously which leads to diseases [12].

3.1. MAPK/RAS Pathogenesis

Mutation of this pathway leads to so many genetic disorders as well. It has some profound effects on CFC, CS, NF1, NS and NSML [13]. **Figure 1** below illustrates the alteration of factors responsible for these disorders. For example, FC is caused by the mutations in BRAF, MEK1 and MEK2. Mutations in KRAS, lead to CFC and NS [14].

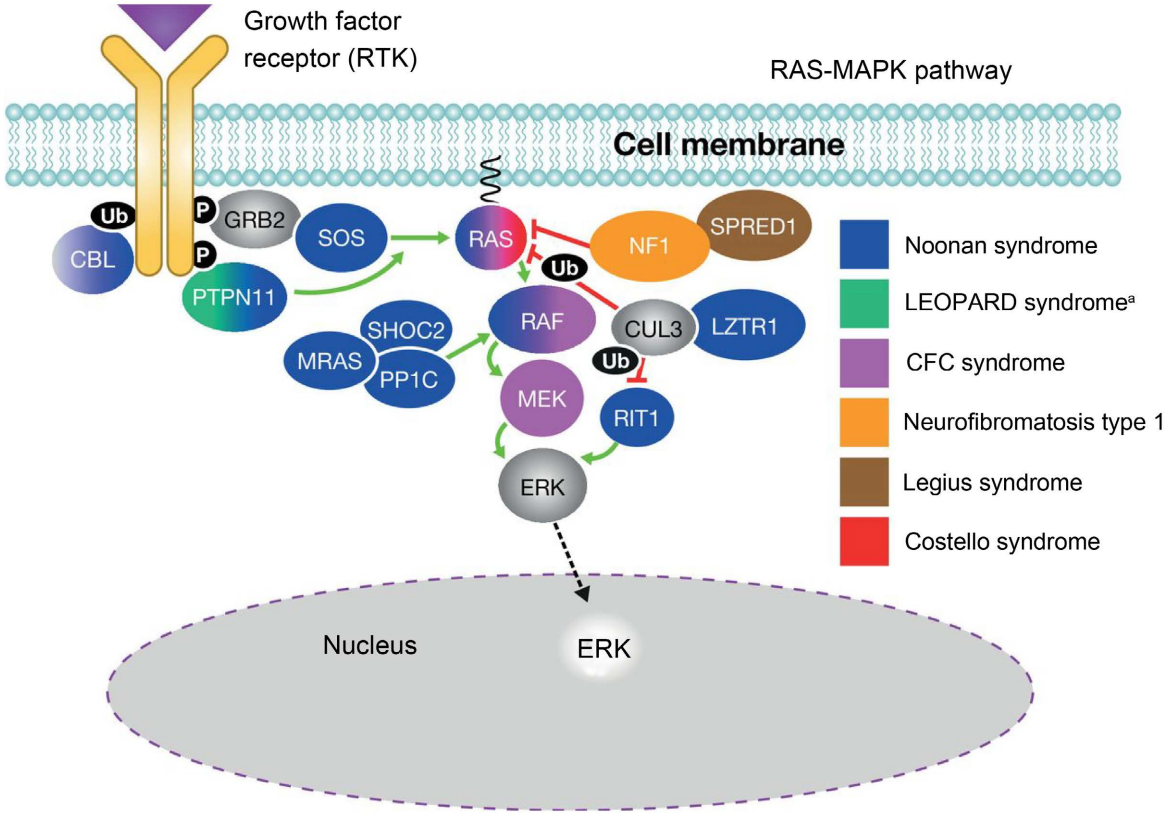

Figure 1. Involvement of MAPK/RAS pathway in genetic disorders [15].

Also, over expression of receptors and mutations in Ras leads to 30% of human cancers [16]. Ras protein activation can constitutively occur due to single point mutations in Ras where GTPase activities become impaired leading to proliferation and carcinoma [17]. Table 2 below indicates the different varieties of carcinoma due to RTK mutation.

3.2. PI3 AKT Pathogenesis

PI3/AKT pathway is negatively controlled by PTEN. Deletion of PTEN and mutation in PI3K1 could be seen in prostate cancer. Through p110, the major sub unit of PI3K1 leads to hyper continuous activation of this pathway which gradually leads to carcinoma [26]. This mutation of PTEN is observed in various types of cancers as shown in Table 3 below.

Clinical trials have elucidated, ovarian cancer and breast cancer mutations in PI3KCA, PI3K, PTEN, p95 and AKT mutation, overexpression of receptors leads to permanent proliferation of cancerous cells [28].

4. Tyrosine Kinases as the Target for Cancer Therapy

The most common type of anti-cancer therapy is conventional chemotherapy

Table 2. Illustrates RTK mutations and their impact on different cancers.

Site of cancer	KRAS frequency of mutation	BRAF frequency of mutation	Reference
Thyroid	1.8% (141/7717)	41.5% (19,297/46,463)	[18] [19]
Skin	2.3% (86/3729)	41.4% (1656/3729)	[20]
Large intestine	34.5% (18,551/53,826)	12.5% (9253/74,074)	[21] [22]
Eye	1.6% (4/258)	10.1% (84/828)	[23] [24]
Bone	1.7% (11/643)	-	[25]

Table 3. PTEN mutation and carcinomas [27].

Tumor type	Site	Range (%)	Average (%)	Loss of heterozygosity (LOH)
Glioblastoma	Brain	17 - 70	48 (107/224)	Mostly LOH
Ductal carcinoma	Breast	15 - 48	37 (37/100)	Mostly LOH
Endometrioid carcinoma	Endometrium	34 - 83	42 (139/334)	LOH and mutation
Adenocarcinoma	Prostate	17 - 41	33 (49/149)	Mostly LOH
Cystadenocarcinoma	Ovary	6 - 45	33 (65/198)	LOH and mutation
Melanoma	Skin	32 - 33	33 (18/55)	Mostly LOH
Carcinoma	Thyroid	37	37 (19/51)	Mostly LOH

which has systemic side effects. Recently, the use of novel molecular targeted therapies has raised the interest of both clinicians and patients [29].

Therapies can target the ligands, receptors, intracellular second messengers and nuclear transcription factors responsible for tumor growth. Ligands can be neutralized before they bind to the receptors. Commonly there are two types of therapies targeted through RTK, small molecule tyrosine kinase inhibitors which are membrane, intracellular targets and monoclonal antibodies. Small molecule tyrosine kinase inhibitors are further divided into 4 types and examples are shown in **Table 4** and **Table 5** [30].

Monoclonal antibodies are commonly used, which are highly specific that binds to the extracellular domain of RTK and secreted protein. These prevent ligand-receptor interaction, dimerization of receptors and activation of pathways. At times, it leads to shedding off the extracellular portion of receptors eventually

Table 4. Types of small molecule tyrosine kinase inhibitors [30].

Types	Description
ATP competitive inhibitors	• Binds to the ATP binding site of the kinase in its active conformation
Inhibitors	• Binds to non-active conformation of ATP bindingsite
Allosteric inhibitors	• Binds to the outside of ATP binding site • Modifies tridimensional structure of the receptor • Disrupt interaction between ATP and its kinase bindingsite
Covalent inhibitors	• Irreversible binding of ATP binding site of kinase

Table 5. Highlights current tyrosine kinase inhibitors targeting receptor tyrosine kinase in cancer therapy [31].

Name	Molecular mass (g/mol)	Selective Target	FDA approved	Cancer (example)
Afatinib	485.94	HER2, EGFR	Yes	Squamous cell arcinoma 0f head and neck, breast cancer
Crizotinib	450.34	MET	Yes	Anaplastic large cell lymphoma, Neuroblastoma
Eroltinib	393.43	EGFR	Yes	NSCLC, AML
Icotinib	391.15	RGFR	Yes	NSCLC
Lepatinib	581.06	HER2, EGFR	Yes	Breast cancer
Lenvatinib	426.85	VEGFR 2,3	Yes	Thyroid cancer

Table 6. Recent FDA approved monoclonal antibodies used in oncology for the cancer treatment [32] [33] [34].

Name	Year	Target	1st approval indication	Mechanism
Denosumab	2010	RANKL	Bone metastasis	Signal Inhibition
Ipilimumab	2011	CTLA-4	Metastatic melanoma	Signal inhibition
Brenfuximab (vedotin)	2011	CD30	Hodgkin's lymphoma	ADC
Pertuzumab	2012	HER2	Breast cancer	Signal inhibition, ADCC
Trastuzumab (ematansine)	2013	HER2	Breast cancer	Signal inhibition, ADCC

controlling the proliferation of cancer cells as shown in Table 6 [31].

5. Ongoing Research on Tyrosine Kinase and Cancer Therapy

Moreover, literature showcases drug resistance as the major challenge for therapy. For example, "Imatinib" is a small molecule tyrosine kinase inhibitor used to treat CML. This binds to the ATP binding side of BCR-ABL protein and inhibits the signal for CML Due to drug resistance and point mutation, BCR-ABL changes its confirmation where "Imatinib" cannot be used longer [35].

If the drug inhibits one pathway, a corresponding and independent pathway can take over carcinogenesis. For example, in drug resistance MAPK/RAS and PI3/AKT pathway alters Hippo pathway responsible for degradation [36]. Therefore, recently scientists have been working on a combination regimen of drug therapy based on different signaling pathways of receptor tyrosine kinase [37].

6. Conclusion

The high prevalence of cancer worldwide opens up gates for therapies and new discoveries. Such that Receptor tyrosine kinases will be a potential target to transit treatment patterns from classical chemotherapy to target therapy. Although scientific research found inhibitors, monoclonal antibodies and target components for these RTK signaling pathways in cancer therapy, mutations by the cancer cells and their resistance to these inhibitors are still a challenge for cancer therapy. Moreover, apart from the classical treatment and prevention, using the receptors like RTK is still a magic bullet in the treatment and prevention of cancer progression.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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List of Abbreviations

ABL: Abelson murine Leukemia
BIM: Bcl-2 like 4
BAX: Bcl-2 associated X protein
BAD: Bcl-2 associated D protein
BCL-2: B cell lymphoma gene 2
BCR-ABL: Bcl-2 like receptor-Abelson Murine Leukemia
BRAF: V-raf murine sarcoma viral oncogene homolog B1
CDK: Cyclin dependent kinases
CFC: Cardio Faciocutaneous syndrome
CS: Cockayne syndrome
CML: Chronic myelogenous leukemia
C-RAF: v-raf 1 murine leukemia viral oncogene homolog C1
ERK: Extracellular signal related kinase
Elf4: Eukaryotic translation initiation factor 2-alphakinase 1-4
FOXO: Forkead homo box type O 3a
FDA: Food and Drug administration
GTP: Guanine Tri phosphate
GDP: Guanine di phosphate
MEK: MAPK/ERK kinase
MTOR: mammalian target of rapamycin
MAPK: mitogen activated protein rapamycin
NF 1: Neurofibromatosis type 1
NS: Noona syndrome
NSML: Noonan syndrome with multiple Lentigines.
PTEN: Protein tyrosine phosphate
PIK3CA: Phosphatidylinositol-4,5-Biphosphate 3-Kinase catalytic subunit alpha
SH2: src homology 2 domain
SYK: Spleen tyrosine kinase
PIP 2: Phosphotidylinositol 4, 5-Bisphasphate
PIP 3: Phosphatidylinositol-Bisphosphate