Chapter

Recent Advances in the Therapeutic Development of Receptor Tyrosine Kinases (RTK) against Different Types of Cancer

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Abstract

Receptor Tyrosine Kinases (RTKs) are an important class of receptors involved in regulating different cellular functions. The usual pathway of RTK activation involves specific ligand binding, dimerization and trans-autophosphorylation. Recently, RTK has been extensively studied as they have potential applications in targeted cancer therapy. RTK-based therapeutic strategies are promising because dysfunction of RTK is connected to a variety of diseases. More specifically, RTK has been widely associated with different types of cancer and related diseases. The chapter aims to cover recent advances and challenges in RTK related research, to get an overview of the problems and possibilities associated with targeted therapy. This will help in deciphering novel therapeutic applications in the future.

Keywords: receptor tyrosine kinase, RTK mutations, cancer, targeted therapy, RTK inhibitors

1. Introduction

A cell is dependent on a wide array of molecules to perform all its activities in a regulated manner. Any disruption in any of the molecules or related pathways can lead to various developmental issues and diseases. Hence, a cell depends on stringent signaling pathways which enables it to grow, proliferate, differentiate, and carry out all physiological processes required for survival and/or apoptosis. One such signaling pathway is the Receptor Tyrosine Kinase (RTK) signaling pathway which is extremely crucial in almost all kind of cells. This pathway usually begins by activation of receptors on the cell membrane, which in turn, undergoes self-phosphorylation and activation of other downstream signaling targets (**Figure 1**). There are various mechanisms by which RTK can elicit its effects on the cell. Any mutation in RTK or its associated targets can be detrimental to the cell, leading to various diseases, including cancer. Thus, identifying these mutations and strategizing therapies targeting such receptors and their associated molecules, can prove to pave the path for creating effective anticancer drugs. Tyrosine kinase inhibitors can also be used to attenuate the increased activity of RTK signaling pathway. A multitude of cancers have been linked to dysregulation of RTK signaling. This chapter covers the current scenario of RTK-associated cancers and the recent therapeutic

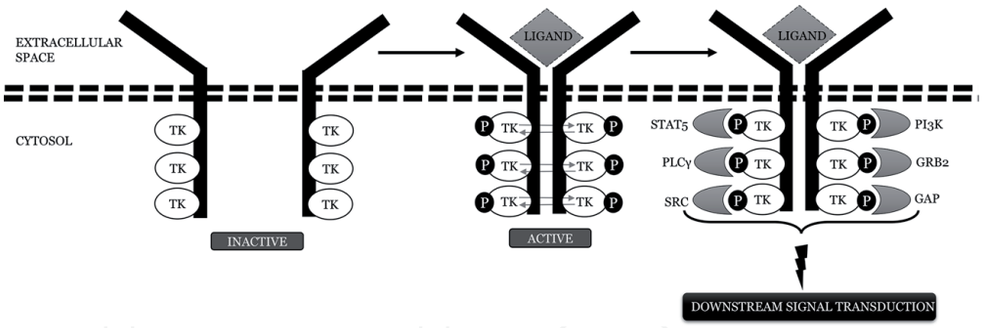

Figure 1.
Mechanism of activation of the tyrosine kinase receptor. Receptor tyrosine kinase exists as monomers in the inactive state. It has an extracellular domain and a cytosolic domain. Upon binding to a specific ligand, it is activated by trans-autophosphorylation of the tyrosine kinase domain. This leads to recruitment of specific adaptor protein(s) and activation of downstream signaling pathways.

strategies, either implemented or having the capacity to be implemented in the future. An understanding of the recent advances in this field has ample potential to investigate the plethora of possibilities ahead.

2. RTK: at the crossroads of cell growth, proliferation and differentiation

Receptor Tyrosine Kinases are a class of very important receptors involved in signaling mechanisms related to cell growth, proliferation, survival and development. Dysregulation of this receptor or its associated molecules has been linked to various diseases, including cancer. Human genome contains around 55 receptor tyrosine kinases (RTK). These RTKs undergo several types of post-translational modifications, some of which include tyrosine phosphorylation, ubiquitination, ectodomain shedding, and regulated intramembrane proteolysis. Structurally RTKs are single-pass membrane proteins that are grouped into subfamilies based on similarity in their extracellular domains. The intracellular kinase domains are in turn, coupled to different extracellular modules. Many RTKs have been reported to be cleaved by gamma-secretase-mediated intramembrane proteolysis. It is a two-step process. In the first step, the RTK ectodomain is released to the extracellular space by proteolytic cleavage called shedding. In the second step, RTK transmembrane domain is cleaved by the gamma-secretase complex. This, in turn, leads to release of a soluble RTK intracellular domain that can translocate to various cellular compartments, such as the nucleus or proteasome, and can also interact with transcriptional regulators and other molecules to induce cell survival, proliferation and differentiation. The tyrosine kinase domain is an integral part of this intracellular domain [1]. The internalization process retains the RTK's transmembrane domain. The endosomal RTK remains active before being recycled or degraded. The transport of RTK from endosome-Golgi-ER to the nucleus is primarily dependent on membranous vesicles and hence, relies on its interaction with the transport complexes like COP-I vesicle complex, Sec61 translocon complex and importin. Nuclear- RTKs have the property of retaining oncogenic properties and can enhance cancer progression. Nuclear-localized RTKs have, in fact, positive correlation with cancer recurrence and therapeutic resistance of cancer patients [2]. It has also been observed that reduced ectodomain shedding and decreased ubiquitination of the cytoplasmic region produce malignant cells. Events like receptor phosphorylation and ubiquitination are reversible, whereas proteolytic cleavage events are irreversible. Any such modification has the potential to alter the subcellular localization of RTKs [3].

The activation of RTK is by dimerization of two monomers and this can either be receptor-mediated or ligand-mediated. The ligands can either be soluble or membrane-embedded. Sometimes, multiple ligands can interact with the same receptor. Such ligands often act as biased agonists and can initiate signaling responses via activation of the same receptor [4]. Activation of RTK involves homodimerization followed by trans autophosphorylation. However, some groups of RTKs can interact with each other even in the absence of ligand, which eventually leads to heterodimerization across sub-families. This results in irreproducibility of data from different experimental sets and hence, is a big hurdle for RTK inhibitors to produce desired therapeutic effects [5]. Both genetic and epigenetic modifications in the genes encoding for RTKs are responsible for activation of growth factor-mediated signaling events. This hyperactivation of RTK mediated signaling cascades can even cause cancer [6].

The degree and duration of RTK signaling plays a pivotal role in determining specific cellular behaviors. The feedback regulation of RTK signaling is critical for determining different diseases. The loss of such feedback mechanism can lead to an aberrant increase in the RTK signaling, resulting in an uncontrolled increase in cell growth, proliferation and survival. Thus, both positive and negative regulators of RTK signaling are crucial in development [7].

The use of Tyrosine Kinase Inhibitors (TKI) remains one of the standard methods of elucidating anticancer effects. The antitumoral properties of TKIs due to induction of apoptosis and cell cycle arrest is a result of tightly controlled events involving different cellular compartments such as endoplasmic reticulum and mitochondria [8].

3. RTK mutations: targets for cancer therapy

Receptor Tyrosine Kinase and its downstream signaling mechanism is crucial for maintaining the integrity of cellular processes, such as growth, proliferation and survival. Any mutation in the RTK or its associated partners can be detrimental to the cell and can even be oncogenic in nature. A mutation which can directly or indirectly lead to upregulation of RTK can eventually result in tumor formation. Recent large-scale genomic studies have highlighted the presence of mutations and alterations in the genes encoding RTKs such as EGFR, HER2/ErbB2, and MET and many other genes. Abnormal RTK activation in human cancers can occur by four major pathways: gain-of-function mutations, genomic amplification, chromosomal rearrangements, and/or autocrine activation [9].

For instance, loss or inactivation of phosphate and tensin homolog (PTEN), leads to overactivation of RTK/PI3K/Akt signaling pathway, eventually leading to tumorigenesis. It has been observed that transcription of PTEN pseudogene, PTENP1, results in sense and antisense transcripts which can, in turn, exhibit post-transcriptional and transcriptional modulation of PTEN expression, respectively. Thus, the effects of the sense and antisense transcripts of PTENP1 on PTEN expression can influence RTK expression and associated signaling pathway, and has promising potential in cancer therapeutics [10]. Another well studied mutant of RTK is MET, which was discovered way back in 1984. The MET RTK and its ligand HGF are key players in more than one type of cancer. High expression of the MET receptor has been shown to correlate with poor prognosis and resistance to therapy. MET exon 14 splicing variants that was initially identified in lung cancer can be treated through various tyrosine kinase inhibitors (TKIs) [11].

Additionally, alternative splicing of RTK pre-mRNA is a novel aspect of study, which can be linked to development of tumor and its maintenance. However, the

exact biological functions of different RTK splice variants and the signals responsible for it is not yet well studied. The mechanism by which these splicing events affect the response of tumor to RTK targeted therapies, and whether these therapies have any effect on the fate of RTK alternative splicing, is a very interesting aspect that can be studied. Moreover, the upstream signals that control their expression in tumors, remain to be understood. More importantly, it remains to be determined whether, and how, these splicing events may affect the response of tumor cells to RTK-targeted therapies, and inversely, whether these therapies may impact these splicing events [12].

An overall understanding of the different mutations and alterations related to RTK, will provide a deeper understanding of the receptor and pathways that have important implications in anticancer therapies. Numerous RTK-targeted therapies have been developed to counteract this hyperactivation.

4. RTK disruption in different types of cancer

Receptor Tyrosine kinases are a class of extremely important receptors, and hence, any issue with its regulation or expression can bring about changes in a cell's growth, survival, differentiation and metabolism. One of the most significant effects of RTK dysregulation is cancer and related phenotypes. RTKs serve as important biomarkers that can help analyze tumor progression and metastasis and determine diagnosis and prognosis in the patients. Different cancers have been observed to have a major link with RTKs. For instance, the Epidermal Growth Factor receptor (EGFR) gene has a tyrosine kinase domain, and somatic mutations within this domain, has been linked to non-small cell lung cancer (NSCLC) progression and are called "EGFR sensitizing mutations". One of its inhibitors, called Raf Kinase Inhibitor Protein (RKIP) has the potential to modulate RTK associated signaling events, such as those controlled by EGFR. It has been reported to have metastasis suppressor role in lung cancer [13].

RTK has also been studied extensively in a complex and heterogenous tumor arising from neural crest derived peripheral neurons, known as neuroblastoma, which sadly accounts for 10–15% of all childhood related cancer deaths. Neuroblastoma tumorigenesis involves a receptor tyrosine kinase known as Anaplastic Lymphoma Kinase (ALK), which is a fusion partner in translocation events related to different types of cancers. RTK translocations are responsible for creating a fusion protein containing a dimerizing partner fused to an RTK kinase domain. This, in turn, leads to constitutive kinase domain activation and results in altered RTK cellular localization as well as upregulation of different downstream signaling. In neuroblastoma, however, the full length ALK RTK is itself mutated [14]. Fortunately, many different RTK inhibitors, that are known to inhibit ALK, have been FDA approved and can be used in ALK-driven neuroblastoma treatment.

Apart from neuroblastoma, another type of cancer-related to the brain is gliomas, representing the most common form of malignant brain tumor. Unregulated RTKs such as MET and EGFR, have a central role in the progression of glioblastoma. Mutations in MET and its various regulatory molecules have been linked to different stages of glioblastoma. MET along with its ligand Hepatocyte Growth Factor (HGF) have been shown to hold importance in proliferation, invasion, migration, angiogenesis, recurrence and therapeutic resistance. Targeting HGF/MET in glioma patients is an important therapeutic strategy [15]. HGF/MET has also been extensively studied and found to be involved in different primary malignant brain tumors such as astrocytomas, glioblastomas,

oligodendrogliomas, ependymomas, and embryonal central nervous system tumors (including medulloblastomas and others) [16].

Another report highlights the relevance of different types of RTKs such as epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor (PDGFR), c-Met, Tie, Axl, discoidin domain receptor 1 (DDR1), and erythropoietin-producing human hepatocellular carcinoma (Eph) in glioma invasion, and how these can act as targets for glioma therapy [17].

Another common RTK that has been observed in different tumor promoting activities, such as cell proliferation and invasion is AXL. It does so by promoting EMT events, metastasis and drug-resistance. It can also modulate tumor microenvironment and corresponding immune response. This RTK is known to be involved in cancer progression of different types of malignancies ranging from hematopoietic cancers to solid tumors. AXL upregulation has been observed in a wide variety of cancer types, such as breast cancer, and is under focus to investigate possible therapeutic implications by its modulation [18]. Downstream signaling pathways of RTKs such as MAPK, PI3K/Akt and JAK/STAT pathways are major players that regulate cancer progression and metastasis, if not regulated [19]. Problems related to proper regulation of RTK signaling pathway has also been noted in Acute Myeloid Leukemia (AML) [20].

Another type of cancer where issues related to RTK signaling are noted, is osteosarcoma. Multi-target tyrosine kinase inhibitors have shown promising effects in the treatment of osteosarcoma, but the exact target is unclear. This is because inhibiting any one type of RTK as a target for treatment of osteosarcoma has not been proven to be effective. Rather, inhibition of multiple RTKs simultaneously show a much better progress in TKI dependent osteosarcoma treatment. This is because receptor tyrosine kinases like MET, IGF-1R, AXL, PDGFRs, KIT, and FGFRs might be relevant but unimportant targets for osteosarcoma treatment [21].

Gastrointestinal stromal tumor (GIST) is also a type of tumor originating from interstitial cells of Cajal in the GI tract, in which genes encoding RTK are mutated. Genes such as KIT and PDGFRA are activated and eventually lead to tumor formation. It has also been noted that RTK inhibitors like imatinib, can significantly act as therapeutic agent in treatment of patients with GIST [22]. Inhibition of downstream signaling like PI3K/AKT/mTOR also exhibit promising outcomes.

RTK dysregulation has also been observed in head and neck cancers, having important implications in tumorigenesis and metastasis. A recent report illustrates the association of non-coding RNAs with RTK and confirms that RTKs and RTK based therapy are superior to other existing therapeutic interventions for HNC [23].

Although issues in RTK regulation are more common in solid tumors, RTK translocations are also observed in hematological malignancies. Fibroblast Growth Factor Receptor (FGFR), Platelet-Derived Growth Factor Receptor (PDGFR), Rearranged during Transfection (RET), Colony Stimulating Factor 1 Receptor (CSF1R), and Neurotrophic Tyrosine Kinase Receptor Type 3 (NTRK3) fusions are some of the common anomalies found in hematopoietic disorders [24].

5. An overview of RTK inhibitors

There have been a wide variety of Receptor Tyrosine Kinase (RTK) inhibitors, many of which have been approved by the FDA. These inhibitors play a significant role in inhibiting the effect of RTK in cells where they are dysregulated, and thereby, providing a strategy to inhibit cell growth and proliferation. As a result, these inhibitors are well known anticancer agents as well (**Figure 2**). One such example is the inhibitor known as Entrectinib (A) (**Figure 2**), which shows massive

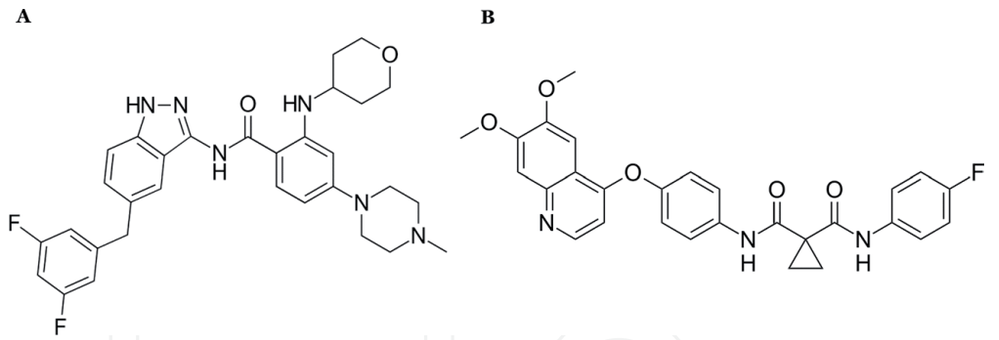

Figure 2.
Structure of potent RTK inhibitors. (A) Entrectinib (B) Cabozantinib.

potential in the treatment of very complex childhood cancer, neuroblastoma. This type of cancer is mainly caused by differential expression of ALK or TRKA/B/C. Entrectinib (RXDX-101) is a pan-ALK, TRKA, TRKB, TRKC, and ROS1 inhibitor with activity against tumors with ALK, NTRK1, NTRK2, NTRK3, and ROS1 alterations in Phase I clinical trials in adults [25]. In June 2019, Entrectinib got its first global approval in Japan, for treating adult and pediatric patients with NTRK fusion-positive and advanced or recurrent solid tumors. It is under regulatory review for the treatment of adult patients with ROS1-positive non-small cell lung cancer (NSCLC). Entrectinib is also under regulatory review in the USA (PDUFA date 18 August 2019) and EU [Priority Medicines (PRIME) designation] for NTRK-positive solid tumors and ROS1-positive NSCLC [26]. Another example of an inhibitor which acts against multiple receptor tyrosine kinases is Cabozantinib (B) (**Figure 2**). This is commercially available as Cabometyx tablet and is used in the treatment of hepatocellular carcinoma (HCC). This inhibitor is usually used in the treatment of patients who are in an advanced stage of cancer and have already been under treatment with the multi-RTK inhibitor sorafenib [27].

6. Promising therapeutic strategies

Receptor Tyrosine Kinases are important regulators of the cell cycle pathway. For a cell to grow and proliferate normally, this receptor plays a major role. Hence, any form of over-expression or overactivity of the RTK or its associated signaling pathway, naturally leads to tumor formation and is well connected with the development of cancer. As a result, RTK and its associated pathways have always been under investigation to find targets in the fight against cancer.

A recent report establishes the relationship between RTK signaling and DNA repair, hinting towards a connection between RTK and the factors involved in the repair pathway. Thus, RTKs can act as potential modulators of the DNA repair pathway and novel therapeutic strategies can be implemented, which will target both DNA repair pathways and RTK mediated signaling pathways [28]. Another report also highlights the link between RTK signaling and DNA repair. Activation of the serine/threonine kinase AKT, also known as protein kinase B (PKB) stimulates DNA repair, like double strand break repair after radiotherapy. Thus, AKT could possibly be a major predictive marker of conventional cancer therapy, molecularly targeted therapy, and immunotherapy for solid tumors. Activated AKT mediates resistance to cancer treatment modalities, such as radiotherapy, chemotherapy, and RTK targeted therapy [29]. Checkpoint inhibitors such as pembrolizumab have proven effective at extending survival for mismatch repair (MMR)-deficient and high microsatellite instability (MSI) metastatic colorectal patients.

Different RTK mutations, deletions, translocations and amplification/over-expressions have been identified and these are currently under study to elucidate their role in cancer. The therapeutic strategies involving RTKs can be classified into small molecule inhibitors and monoclonal antibodies [30].

The presence of RTK fusions is by large, responsible for providing acquired resistance to different therapies. This poses a challenge in the administration of Tyrosine Kinase Inhibitors as anticancer treatment and thus, is a field that requires a lot of attention. Recent reports have come up with the different strategies that can be beneficial in solving this issue [31].

Another interesting and emerging study reveals the connection between EGFR, a common RTK that is dysregulated in different malignancies, and autophagy. In fact, autophagy upregulation as well as downregulation has been observed in several cancers, highlighting its oncogenic and tumor suppressor properties in tumor progression. EGFR has the potential to determine whether autophagy will have a cytotoxic or cytoprotective effect. The EGFR-mediated pathways or proteins involved in autophagy regulation include (a) the EGFR-mTOR pathway; (b) the EGFR-RAS pathway; (c) EGFR-Beclin1; [8] the EGFR-STAT3 pathway and (e) EGFR-LAPTM4B (oncoprotein lysosomal-associated transmembrane protein 4B). Thus, understanding the regulation of autophagy by EGFR can prove to be a highly efficient strategy to identify potential cancer therapeutic targets [32]. Anti-epidermal growth factor receptor (anti-EGFR) agents panitumumab and cetuximab, combined with chemotherapy, have also prolonged the survival of cancer patients.

One of the most promising therapeutic strategy which is widely established and used is immunotherapy. It has proved its worth by improving the prognosis of many patients with a broad variety of hematological and solid malignancies. The importance of immunotherapy has been acknowledged by the Nobel prize for physiology or medicine 2018 awarded for the discovery of cytotoxic T-lymphocyte-associated protein (CTLA-4) to James P. Allison and programmed cell death protein 1/programmed cell death protein ligand 1 (PD-1/PD-L1) to Tasuku Honjo [33].

Epithelial-mesenchymal transition (EMT) is a very important event in the prognosis of malignancy. It has been studied that a receptor tyrosine kinase AXL can directly affect the mesenchymal state, making the tumor more aggressive and drug-resistant. The inhibition of AXL has come up as a promising therapeutic strategy in reversing EMT resensitization to other tyrosine kinase inhibitors, mitotic inhibitors, and platinum-based therapy. Therefore, novel ways to inhibit AXL can be used as an effective therapeutic strategy against different types of cancer [34]. AXL receptor tyrosine kinase (RTK) and its ligand, growth arrest-specific protein 6 (Gas6), have been known to be involved in different malignancies and autoimmune disorders. Several molecules are presently under investigation, which can aid in targeting the AXL/Gas6 molecular system, thus providing therapeutic and diagnostic applications [35].

Apart from the inhibitors that directly target the RTK and its associated molecules, some molecules are naturally present with antitumor properties. One such molecule is decorin, which is present in the tumor microenvironment. This molecule is prototype member of the SLRP family found in a variety of tissues and is expressed in the stroma of various forms of cancer. Decorin has recently gained a lot of attention because of its effects in inflammation, fibrotic disorders, and cancer. Since it is present in the tumor microenvironment, it has been proposed to act as a "guardian from the matrix." Soluble decorin has a pan-RTK inhibiting property and can target a few RTKs, including EGFR, Met, IGF-IR, VEGFR2, and PDGFR. Decorin/RTK interaction can induce caveosomal internalization and receptor degradation. Additionally, this interaction can trigger cell cycle arrest

and lead to apoptosis, and can induce conserved catabolic processes, such as endothelial cell autophagy and tumor cell mitophagy. Antimetastatic and antiangiogenic processes have also been reported to be induced by decorin/RTK interaction. Due to such diverse plethora of anticancer effects, decorin is a promising candidate for combatting cancer, especially the cancer types where the major issue is with RTK signaling [36].

Combinations of immunotherapies, RTKs, monoclonal antibodies, and cytotoxic drugs are being investigated to provide broad-spectrum protection against relapse by simultaneously targeting many cancer hallmarks [37].

7. Challenges in RTK related research

Despite the huge potential and success of RTK based targeted cancer therapy, there remain some challenges in this field. One of the major challenges is reducing the off-target effects of Tyrosine Kinase Inhibitors. This non-specificity can lead to deleterious effects on normal cells as well. A possible solution to this challenge can be TKIs-based nanodelivery systems, that will specifically target tumor cells [38]. Another common challenge faced by any anticancer drug is the induction of chemo-resistance during therapy. Patients may invariably develop resistance to these therapies, leading to recurrence. Research that will aim in dealing with chemoresistance by manipulating specific molecules related to it, can have potential role in overcoming this challenge [39]. Thus, increasing target specificity and decreasing drug resistance are the major challenges in RTK related research, along with identification of novel TKIs.

8. Conclusion

This chapter covers the recent advances made in the field of signaling biology, mainly Receptor Tyrosine Kinase-mediated signaling. The structural and functional aspects of the receptor, modes of its activation and current research-based on it has been discussed. Additionally, information related to RTK mutations and disruptions in different types of cancers, gives a better understanding of the different anticancer therapeutic strategies that have come up in the form of inhibitor molecules and drugs. The scope of these receptors is huge if they can be exploited further, along with identification of other novel mutations associated with cancer, and their targets. Sequencing data based on different types of cancer cells, including hematological and solid tumors, can provide a clear picture of the RTK associated genes that are either upregulated or downregulated in different diseases. These studies will open new avenues because different inhibitors/activators or drugs that can target such RTK or its associated molecules, can either be extracted from natural sources or designed in the laboratories. This, in turn, has the potential of targeted therapies and may prove beneficial in the treatment of different types of diseases including cancer.

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