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Introductory Chapter: Tyrosine Kinases as Drug Targets in Cancer Treatment

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1. Introduction

A kinase is an enzyme that catalyzes the transfer of phosphate moieties from high-energy, phosphate-donating molecules (i.e., ATP) to specific substrates that include proteins, lipids, carbohydrates, and nucleotides. The protein kinases act on proteins, via phosphorylating on serine/threonine, tyrosine, or histidine residues; make up the majority of all kinases; and are the most widely studied. Together, protein kinases and phosphatases play a major role in protein and enzyme regulation as well as cellular signaling pathways [1]. More than 90 protein tyrosine kinases (PTKs) have been found in the human genome; 58 PTKs of about 20 families are receptor tyrosine kinases (RTKs), which are the high-affinity cell surface receptors for many growth factors, cytokines, and hormones including EGFR, PDGFR, IGFR, Eph, RET, and DDR; the others are non-receptor tyrosine kinases (nRTK), which are cytosolic enzymes and function in signal transduction pathways in activated immune cells [2]. Examples of nRTKs include Src, Abl, ZAP70/Syk, and JAKs and are separated into nine families. PTKs function as an “on” or “off” switch in many cellular functions; the abnormal activity of PTKs is responsible for many types of cancer development and progression [2–4].

Recent data from large-scale consortia such as the Cancer Genome Atlas (TCGA) [5] and the International Cancer Genome Consortium (ICGC) [6] have revealed many new mutations in kinases and authorized a robust delineation of the spectrum of activating kinase mutations in cancer by statistical analysis [7]. The oncogenic activation of PTKs is derived from many types of genetic and epigenetic changes, such as (1) activating point mutations, (2) chromosomal amplification, (3) chromosomal alterations such as translocations or deletions, (4) epigenetic changes, and (5) other alterations from indirect regulatory factors including activation of a kinase transcription factor, inactivating mutations of negative regulators, RNA alternative splicing, etc. [8–10]. In fact, these multiple layers of events that result in constitutive activation of PTK pathways in cancer represent important and tractable opportunities for therapeutic intervention. Tyrosine kinase inhibitors (TKIs) aiming at various PTKs have thus been generated with potent anticancer activities. It is estimated that over 10,000 patents have been documented in the USA for kinase inhibitors including tyrosine and serine/threonine kinase inhibitor drugs since 2001 [11]. Drugs have been developed to target the extracellular domain or the catalytic domain, thus inhibiting ligand-binding, receptor oligomerization [12]. Herceptin, a monoclonal antibody that is capable of binding to the extracellular domain of RTKs, has been used to treat HER2-overexpressing breast cancer [13]. Usually, the monoclonal antibodies are used for the targeted blockade of RTK,

which block the extracellular domain of the receptor and inhibit the binding of a ligand. For the specific inhibition on nRTKs, however, TKIs are used to block the signaling transduction cascade either at the intra-cytoplasmic level or directly block the nRTKs [14]. Reasonably, protein kinase inhibitor drugs target and act upon signaling pathways that have gone awry in a given cancer, whereas all traditional chemotherapy drugs work on cell division and growth mostly leading to the destruction of healthy cells as the main problems in treatment of cancer patients. In comparison, the treatment with TKIs has fewer side effects and less time for the patient in the hospital. More favorably, in many cases it is feasible to screen tumor biopsies to see if a particular patient's cancer has a mutation that can be targeted by TKI drugs [2, 12].

Up to date, the US Food and Drug Administration (FDA) has approved more than 30 kinase inhibitor drugs for cancer therapy; most of these target kinases are PTKs including ALK, BCR-Abl, BTK, c-Met, EGFR family, JAK family, MEK1/2, PDGFR α/β , RET, Src family, and VEGFR family; only B-raf and CDK family are targets of serine/ threonine kinases [11]. The aberrant PTKs promote key events during cancer development and progression including: (1) Tumor initiation and tumor transformation process. Examples of such PTKs include JAK2, ALK, IGF-1R, c-Kit, FGFR1-4, c-Met, c-Ret, c-Src, etc. (2) Formation of oncogenic kinase pathways for tumor cell survival and proliferation. The typical example is EGFR whose oncogenic alteration composite is ~45% of mutations in the PTK domain and aberrant alterations on other cytoplasmic signaling pathways such as MEK1/2, mTOR, and many other serine/threonine kinases. (3) The oncogenic kinases over-expressed in both tumors and the surrounding tissues which are essential for tumor maintenance in the host. These include VEGFR, FGFR, BDNF receptor TrkB, etc. (4) Aberrant activation leading to over-expression of RTK which is a hallmark of cancer. These aberrant RTKs are rigorously targeted in cancer, mostly growth factor receptors including EGFR, VEGFR, PDGFR, etc. Several small molecule inhibitors and monoclonal antibodies have been approved by FDA on various RTKs for cancer therapies. Presently, important TKI drugs include imatinib (targeted at PDGFR, KIT, Abl, Arg), sorafenib (targeted at Raf, VEGFR, PDGFR, Flt3, KIT), lapatinib (targeted at EGFR, ErbB2), etc. [7, 11].

However, despite encouraging results, the problems with drug resistance, toxicity, and even limited efficacy present critical challenges in both clinical and experimental oncology. Kinase inhibition induces a strong selective pressure for cells to acquire resistance to the therapy through kinase mutations [15]. Therefore, the treatment and pathological behaviors of cancer are further complicated by secondary mutations that occur in different kinases [16]. Moreover, data collected from different centers around the world are inconsistent due to complexity of patients' biopsies in temporal and spatial variations, as well as differences in data analysis and interpretation. Strategically, the next generation of inhibitor drugs is developed and applied with proposed better efficacy. Furthermore, drug combination therapies are designed and used in the treatment; some of them achieve improved results, yet others are likely biased toward validating well-designed targets, thereby limiting their capacity to prioritize novel drug targets [11]. Furthermore, many kinase inhibitors are associated with toxicities and off-target effects such as cardiotoxicity, hypertension, hypothyroidism, skin reactions, and proteinuria [17, 18]. Especially, EGFR inhibition is associated with dermatological problems, VEGFR inhibition with cardiotoxicity, and HER2 and ALK inhibition with gastric irregularities and dermatological issues, and BCR-ABL inhibition causes cytopenia, in addition to cardiotoxicity and cardiac complications [19, 20].

Kinase inhibitor drug discovery has progressed dramatically in the past decade; besides cancer treatment, kinase inhibitor drugs begin to be tested for the treatment

of other diseases such as autoimmune diseases and inflammatory disorders [21]. A few kinase inhibitors are first-line drugs in cancer treatment; currently, an equilibrium which has been attained as traditional chemotherapy is still in use and in combination with target therapy. More and more molecules are selected as potential targets and developed as drug candidates; some of them are successfully applied in the clinics as imatinib, yet others are failed at some point during development [22]. Up to date, however, only a small fraction of the human kinome is being targeted, and therefore, besides protein kinases, lipid kinases and carbohydrate kinases, as well as phosphorylases and phosphatases, should be studied in analyzing the efficacy and resistance in cancer-targeted therapies. In future, an important strategy required for future development is to understand the basis of unexpected toxicities related to kinase inhibitors. Furthermore, there is a need to develop sophisticated modeling testing of chemotherapy efficacy and resistance in response to kinase inhibitors; this will help to overcome kinase resistance and allow for the systematic use of combinations of kinase inhibitors. Additionally, advanced high-throughput cell-based screening using well-defined phosphorylation readouts should be established.

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