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REVIEW ARTICLE

Tyrosine kinases: Structural insights and mechanistic roles in cancer progression and therapeutics

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Abstract

Protein tyrosine kinases (PTKs) are key enzymes of cellular signaling, regulating key processes such as proliferation, differentiation, migration, metabolism, and apoptosis. Tyrosine kinases (TKs) modulate protein functions in normal and disease states by phosphorylation of tyrosine residues on target proteins. In this critical role, dysregulation of TKs is directly linked with disease progression, particularly in cancer, therefore making TKs an attractive target for therapeutic intervention. The PTK family is broadly classified into receptor TKs (RTKs) and non-receptor TKs (NRTKs), having variation at both structural and functional levels. RTKs are membrane-bound kinases that initiate intracellular signaling when they react with extracellular ligands, whereas NRTKs within the cytoplasm or nucleus convey intracellular signaling upon receptor activation. This paper aims to review the organization, mechanistic activity, and therapeutic potential of PTKs, with a particular focus on epidermal growth factor receptor and proto-oncogene tyrosine-protein kinase (Src) as representatives of RTK and NRTK, respectively. In addition, this review also focuses on addressing emerging strategies to enhance tyrosine kinase inhibitor efficacy and overcome acquired resistance in cancer therapy.

Keywords: Protein tyrosine kinases; Epidermal growth factor receptor; Receptor tyrosine kinases; Non-receptor tyrosine kinases; Cancer; Src kinase; Exo-site

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1. Introduction

Tyrosine kinases (TKs) are crucial enzymes involved in signal transduction that regulates key cellular processes such as proliferation, differentiation, migration, metabolism, and apoptosis.[1-3] By catalyzing the phosphorylation of tyrosine residues in target proteins, kinases mediate vital cellular communication and maintain homeostasis.[4] Phosphorylation functions as a post-translational modification that is essential for normal cellular processes, but its dysregulation can cause disease, including cancer.[5] Unusual activation of protein TKs (PTKs) is usually associated with disease progression and therapy resistance, while

making them critical targets for therapeutic interventions, particularly in cancer treatment.[6,7]

The PTK family is diverse, with members varying in structure and function.[8] These kinases are classified into two major subgroups: receptor TKs (RTKs) and non-receptor TKs (NRTKs).[7,9] RTKs are membrane-bound enzymes that transmit extracellular signals such as growth factors, cytokines, and hormones to the cytoplasm and nucleus, initiating a cascade of cellular responses.[4,7] The key function of RTKs is to rapidly and reversibly phosphorylate protein substrates, which leads to alterations in protein conformation and interaction, driving various cellular processes such as growth and survival.[10] On the other hand, NRTKs lack extracellular and transmembrane domains and are found in the cytoplasm or nucleus. These kinases are involved in mediating intracellular signals, often in response to receptor-dependent activation at the cell membrane.[7,11] While RTKs and NRTKs function similarly by regulating crucial cellular processes, including cell division, growth, and immune responses, their structures are strikingly distinct.[7,12] Due to their essential roles in cellular signaling, both RTKs and NRTKs are critical in the regulation of various physiological functions and are often implicated in the progression of cancers when their activation becomes dysregulated.[13] The discovery of the Src oncogene and the identification of the epidermal growth factor receptor (EGFR) as the first RTK laid the foundation for understanding the role of TKs in cancer.[14] So far, over 90 TKs have been identified, and these enzymes are now recognized as pivotal players in cellular signaling circuits that contribute to cancer development.[15] Hence, TKs represent a significant portion of oncoproteins, and targeting these for therapeutic development is a promising strategy in the treatment of cancers associated with their dysregulation.[6] This review focuses on a deeper structural and mechanistic understanding and therapeutic implications of PTKs, using EGFR and Src as representative models of RTKs and NRTKs, respectively. In addition, the current review also emphasizes recent developments aimed at overcoming resistance to tyrosine kinase inhibitors (TKIs).

2. Classification of PTKs

As described above, PTKs are primarily classified as RTKs and NRTKs.[9] Based on the composition of the extracellular regions, the 58 identified RTKs in humans are further categorized into 20 distinct families. A brief introduction and description of each of the distinct RTK families is presented in Table 1.

The epidermal growth factor family (EGF) includes epidermal growth factor receptor (EGFR), human epidermal growth factor receptor (HER)1, HER2, HER3, and HER4. These receptors are often overexpressed in epithelial tumors, such as colorectal, head and neck, non-small cell lung, breast, pancreatic, and renal cell cancers.[17] The insulin growth factor (IGF) and insulin receptor (InsR) family consists of the IGF1R and InsR receptors. Both

Table 1. RTKs' classification is based on the sequence of the kinase domain

Class	Family	Receptors
I	EGF/ ErbB	EGFR, ErbB2/HER2, ErbB3/HER3, ErbB4/HER3
II	Ins	InsR, IGF1R, InsRR
III	PDGF	PDGFRα, PDGFRβ, CSF1R, KIT, FLT3
IV	VEGF	VEGFR1/Flt1, VEGFR2/KDR, VEGFR3/Flt4
V	FGF	FGFR1, FGFR2, FGFR3, FGER4
VI	PTK7	PTK7/CCK4
VII	TRK	TRKA, TRKB, TRKC
VIII	ROR	ROR1, ROR2
IX	MuSK	MuSK
X	HGF	MET, MST1R (RON)
XI	TAM	AXL, MER, TYRO3
XII	TIE	TIE1, TEK (TIE2)
XIII	Eph	EphA1-8, EphA10, EphB1-4, EphB6
XIV	RET	RET
XV	RYK	RYK
XVI	DDR	DDR1, DDR2
XVII	ROS	ROS
XVIII	LMR	LMR1, LMR2, LMR3
XIX	ALK	LTK, ALK
XX	STYK1	STYK1

Note: Adapted and modified from ref.[16]

Abbreviations: RTKs: Receptor tyrosine kinases; EGF: Epidermal growth factor; EGFR: Epidermal growth factor receptor; HER2: Human epidermal growth factor receptor; Ins: Insulin; InsR: Insulin receptor; PDGF: Platelet-derived growth factor; PDGFR: Platelet-derived growth factor receptor; CSF1R: Colony-stimulating factor 1 receptor; KIT: KIT Proto-oncogene receptor; FLT3: FMS-like tyrosine kinase 3; VEGF: Vascular endothelial growth factor; VEGFR: Vascular endothelial growth factor receptor; FGF: Fibroblast growth factor; FGFR: Fibroblast growth factor receptor; PTK7: Protein tyrosine kinase-like 7; CCK4: Colon carcinoma kinase 4; TRK: Tropomyosin receptor kinases; ROR: RTK-like orphan receptor; MuSK: Muscle-specific kinase, HGF: Hepatocyte growth factor; MET: Mesenchymal-epithelial transition; MST1R: Mesenchymal-epithelial transition 1 receptor; RON: Recepteur d'Origine Nantais; TAM: TYRO3, AXL, MER; TIE: tyrosine kinase with immunoglobulin-like and EGF-like domains; Eph: Erythropoietin-producing hepatocellular; RYK: Receptor like tyrosine kinase; DDR: Discoidin domain receptor; ROS: Reactive oxygen species; LMR: Lemur receptor kinases; ALK: Anaplastic lymphoma kinase; LTK: Leukocyte tyrosine kinase; STYK: Serine/threonine/tyrosine kinase; ErbB: Erythroblastic leukemia viral oncogene homolog; RET: Rearranged during transfection.

IGF1 and IGF2 are capable of binding to and activating the IGF1R transmembrane receptor kinase. However, when IGF2 binds, it does not activate any downstream signaling pathways because the IGF2R lacks the kinase structural domain necessary for this activation.[18] Platelet-derived growth factor receptor (PDGFR), colony-stimulating factor 1 receptor (CSF1R), KIT proto-oncogene receptor, and FMS-like tyrosine kinase 3 receptors are critical for various cellular processes.[19] Platelet-derived growth factor (PDGF) is essential for tissue growth, division, and blood vessel formation. CSF1R, secreted by cancer cells to evade immune detection, promotes the growth and recruitment of tumor-associated myeloid cells, contributing to poorer survival in many cancers.[20] The vascular endothelial growth factor (VEGF) receptor (VEGFR) family—VEGFR-1, VEGFR-2, and VEGFR-3—regulates processes such as cell migration, angiogenesis, and metabolic homeostasis.[21] Likewise, the fibroblast growth factor receptor (FGFR) family, including FGFR1-4, plays a role in tissue repair, regeneration, and the growth and differentiation of cells during development and organ formation.[22] Protein tyrosine kinase-like 7 and colon carcinoma kinase 4 receptors are involved in epithelial cell polarization and brain structure formation.[23] These receptors are catalytically active protein kinases and play roles in the Wnt and VEGF signaling pathways.[24] The neurotrophin receptor kinases family includes tropomyosin receptor kinases (TRK) A, TRKB, and TRKC receptors, which are vital for the proliferation and migration of the nervous system.[25] TRKA responds to nerve growth factor, TRKB to brain-derived neurotrophic factor, and TRKC to neurotrophin-3.[26] The RTK-like orphan receptor (ROR) family includes ROR1 and ROR2 receptors. ROR1 acts as a substitute receptor and co-receptor for Wnt signaling, regulating cell division, polarity, and tissue maintenance.[27] In contrast, ROR2's role in tumor development varies depending on the tumor type or stage; it can either repress or activate tumor growth through atypical Wnt signaling.[28] The muscle-specific kinase receptor is essential for the formation and organization of neuromuscular junctions in skeletal muscle.[29] The hepatocyte growth factor (HGF) receptor family includes mesenchymal-epithelial transition (MET) factor and Recepteur d'Origine Nantais receptors. When HGF binds to MET, it activates the proliferation, migration, and morphogenesis of epithelial cells.[30] The TYRO3, AXL, and MER receptors are activated by the vitamin K-dependent proteins Gas6 and protein S, regulating cell proliferation, survival, adhesion, and migration.[31] They also have anti-inflammatory properties and are implicated in carcinogenesis in various malignancies.[32] The tyrosine kinase with immunoglobulin (Ig)-like and EGF-like domains (TIE) receptor family, consisting of TIE1 and TIE2, regulates angiogenesis and lymphangiogenesis.[33] The erythropoietin-producing hepatocellular (Eph) receptor family (EphA1–A10, EphB1–B6) controls angiogenesis, cell migration, patterning, and neuronal formation.[34] The RET receptor, activated by glial cell-derived neurotrophic factor ligands, is crucial for cell proliferation, neuronal navigation, migration, and differentiation.[35] The receptor tyrosine kinase is characterized by extracellular Wnt-binding domains and is closely associated with Wnt signaling.[36] The discoidin domain receptor (DDR) family, which includes DDR1 and DDR2, regulates cell adhesion, proliferation, and metalloproteinase expression.[37] DDR1 also promotes tumor cell invasion and enhances the survival of tumor stem cells in collagen-rich environments.[38] The reactive oxygen species (ROS) receptor family is present in various malignant tumors, making it a promising target for anticancer drugs.[38] Lemur receptor kinases are linked to cancer and influence multiple signaling pathways involved in cell proliferation, migration, and invasiveness.[39] The anaplastic lymphoma kinase (ALK) receptor family includes ALK and leukocyte tyrosine kinase.[40] *ALK* gene fusion is linked to the formation of various tumors.[41] In addition, the serine/threonine/tyrosine kinase receptor plays a role in cellular processes such as proliferation, differentiation, and survival.[12]

Non-receptor TKs (NRTKs) include Ack, Janus Kinase (Jak), feline sarcoma (Fes), focal adhesion kinase (Fak), Tec, sarcoma (Src), C-terminal Src kinase (Csk), Abelson (Abl), and spleen tyrosine kinase (Syk) kinases.[42] These NRTKs typically consist of the N-terminal kinase domain (KD), which is around 300 residues long, and the C-terminal region, which contains several functional domains.[43] NRTKs share significant sequence similarity within their KDs, and their catalytic domains are like those of Ser/Thr protein kinases.[44] In addition to their catalytic domains, NRTKs also feature non-catalytic domains that regulate their activity.[45] The classification of NRTKs into distinct families is based on molecular analysis of their domain structures, variations in amino acid sequences, and genomic organization of the KDs.[16] Below is a brief overview of the most common NRTK families.

The activated Cdc42-associated kinase (ACK) is a large protein of 120 kDa whose kinase activity can be mediated by the phosphorylation of its tyrosine residues.[46] Ack1 is a non-receptor tyrosine kinase with a unique multidomain structure, including an Src homology 3 (SH3) and Cdc42/Rac interactive binding (CRIB) domain that regulates cellular functions such as migration and adhesion and plays a critical role in cancer progression.[47] Furthermore, Ack1 promotes tumor growth, resistance to chemotherapy, and recurrence through gene amplification, mutations,

and epigenetic regulation.[48] The Jak/Janus family consists of four kinases (JAK1, JAK2, JAK3, and TYK2), each with two KDs, one functional and one pseudo-kinase.[49] These kinases are activated by cytokine receptor ligation, leading to transphosphorylation and downstream signaling.[50] JAKs play crucial roles in immune cell regulation and tumor development through the JAK-STAT pathway. JAK3 is primarily found in hematopoietic cells, while other JAKs are involved in diverse cytokine signaling processes.[51] Fes and Fes-related (Fer) kinases are a subgroup of NRTKs with similarities to viral oncogenes from Fes virus and avian Fujinami poultry Src virus.[42] Fes kinases have a unique Fes/CIP4 homology (FCH) domain, coiled-coil motifs, an Src homology 2 (SH2) domain, and a C-terminal KD.[52] Fes and Fer kinases are implicated in cancer progression, with Fes playing a role in cell signaling pathways that influence cell migration, proliferation, and survival, contributing to tumorigenesis.[53] The Fak family includes Fak, Pyk2, Cak-beta, Cadtk, Raftk, and Fak2, with varying expression in organs such as the brain, liver, and hematopoietic cells.[54] Fak family kinases feature a FERM domain that mediates interactions with integrins and RTKs and a C-terminal FAT region involved in focal adhesion targeting. Fak plays a crucial role in tumor cell signaling, including transcriptional regulation within the tumor microenvironment (TME). Overexpression of Fak is linked to aggressive cancers, including breast, colon, and ovarian, and is associated with metastasis and poor prognosis.[55] The Tec family consists of five NRTK members, including Tec, Itk, Btk, Txk, and Bmx, characterized by several conserved domains, such as a pleckstrin homology domain involved in membrane association, a Tec homology domain, which includes a zinc-binding region, a SH3 domain that regulates protein-protein interactions, an SH2 domain that interacts with phosphorylated tyrosine residues, and a catalytic KD.[56] Tec kinases are involved in immune cell signaling, with specific expression in T, B, and natural killer cells.[57] The Src family is one of the largest NRTK families that include eight members, such as Fyn, Yes, Fgr, and Lyn, divided into two subfamilies: Src-A (Fgr, Fyn, Src, Yes) and Src-B (Blk, Hck, Lck, Lyn).[58] These kinases share a similar structure with Src homology 4 (SH4), SH3, SH2, and KDs but differ in their C-terminal regulatory regions.[59] Src family kinases (SFKs) are involved in diverse cellular processes, with distinct expression patterns in hematopoietic and other tissues.[60] Fyn-related kinase (FRK) is a member of the breast tumor kinase family, closely related to SFKs.[61] FRN kinases feature an SH3, SH2, and KD but lack the N-myristoylation site, which prevents membrane localization and allows nuclear localization.[62] Unique to FRK and inhibitory tyrosine kinase (IYK) kinases is the presence of a nuclear localization signal (NLS) within the SH2 domain.[63] The NLS is a bipartite motif that enables nuclear targeting and functional regulation in the cell.[64] The Abl family includes Abl and Arg kinases, which are widely expressed, with high levels in the thymus, spleen, and brain.[65] Both kinases have structures similar to Src family members but feature a unique C-terminal actin-binding domain and nuclear localization signals.[66] Abl activation, through mutation or phosphorylation, is linked to leukemia and solid tumors such as brain, lung, and prostate cancers.[67] The Syk family includes Syk and zeta-chain-associated protein kinase 70 (ZAP70) kinases, which share a similar structure containing two SH2 domains followed by a catalytic KD.[68] These kinases are cytosolic proteins lacking fatty acid modification sites, and upon cell stimulation, Syk and Zap70 translocate to immune receptor complexes at the membrane to trigger downstream signaling.[69] A tabular representation of kinases that play a significant role in various cancer types is represented in Table 2.

3. Structural and regulatory mechanisms of TKs

PTKs play a critical role in cellular signaling pathways, and their catalytic activity is tightly regulated. Numerous atomic structures of PTKs reported in the literature have provided structural and mechanistic insights into the regulation of both receptor and non-receptor PTKs.[89] As several PTKs are available in the Protein Data Bank (PDB), the current review will focus on EGFR kinase as a representative of receptor PTK and Src for non-receptor PTKs.

3.1. PTK domain architecture

RTKs are composed of three main regions: a large extracellular region, which binds to polypeptide ligands, a transmembrane helix, and a cytoplasmic region, which possesses tyrosine kinase activity. The extracellular region of RTKs is classically composed of a diverse array of distinct globular domains, including Ig-like domains (domain-1), fibronectin type-III-like domains (domain-2), cysteine-rich domains (domain-3), and EGF-like domains (domain-4). In the case of EGFR kinase, the extracellular region includes amino acids 1–165 (domain-1), 166–310 (domain-2), 311–480 (domain-3), and 481–621 (domain-4). However, the cytosolic region of RTKs domain organization is simple, consisting of the juxtamembrane region (amino acids 643–685), immediately followed by the transmembrane helix, a tyrosine KD (amino acids 686–952), and a carboxy region (amino acids 953–1186) (Figure 1A-C). Unlike RTKs, the extracellular and transmembrane regions in NRTKs are absent, and most of the NRTKs are present in the cytosol. The NRTKs comprise intrinsically disordered regions (IDR) and folded domains. At the N-terminus IDR region, unique myristoylated SH4 fragments, a smaller SH3 domain (~60

Table 2. Summary of cancer-associated tyrosine kinases

Class of tyrosine kinase	Cancer type and mechanism
EGFR (HER1, HER2, HER3, HER4)	Epithelial tumors in lung, breast, and colon[17,70]
VEGFR-1 to -3	Regulate angiogenesis and cell migration in tumors[21,71,72]
FGFR-1 to -4	Tissue cancer[22]
TRKA, TRKB, TRKC (NTRK family)	Neuronal cancer[25,73]
RET	Implicated in multiple cancers[35,74]
RYK	Contributes to tumorigenesis[36,75]
DDR1, DDR2	Regulate adhesion, invasion, and survival in collagen-rich tumors[37,76,77]
ROS	Present in many cancer types[38]
LMTK/LMR	Cancer-linked; influences proliferation, migration[78,79]
ALK, LTK	Fusion-driven cancers (e.g., ALK fusions in lymphoma, lung cancer[40,41,80]
STYK	Involved in proliferation and survival; emerging as a cancer target[81]
Ack1	Promotes tumor growth, chemoresistance, gene amplification[45,82]
JAK1, JAK2, JAK3, TYK2	Crucial for immune modulation in cancers[83]
Fes, Fer	Signal for migration, survival; linked to oncogenesis[84]
FAK family	Adhesion, motility; high expression in aggressive tumors[85,86]
Src family	Major signaling mediators; upregulated in various tumors[60]
Abl, Arg	Leukemia[67,87,88]
Syk, Zap70	Hematologic cancers[69]

Abbreviations: EGFR: Epidermal growth factor receptor; HER: Human epidermal growth factor receptor; VEGFR: Vascular endothelial growth factor receptor; FGFR: Fibroblast growth factor receptor; NTRK: Neurotrophic tyrosine receptor kinases; TRK: Tropomyosin receptor kinases; RYK: Receptor tyrosine kinase; DDR: Discoidin domain receptor; ROS: Reactive oxygen species; LMTK/LMR: Lemur receptor kinases; ALK: Anaplastic lymphoma kinase; LTK: Leukocyte tyrosine kinase; STYK: Serine/threonine/tyrosine kinase; Fes: Feline sarcoma; Fer: Feline sarcoma-related; JAK: Janus Kinase; FAK: Focal adhesion kinase; Src: Sarcoma; Abl: Abelson; Syk: Spleen tyrosine kinase; RET: Rearranged during transfection; Ack1: Activated Cdc42-associated kinase; Arg: Abl-related gene; Zap70: Zeta-chain-associated protein kinase 70.

residues), a short (SH2 ~100 residues), SH2 kinase linker, catalytic tyrosine-protein KD (Src Homology 1 [SH[1]), and a short intrinsically disordered C-terminal tail. While the KD has a catalytic function, the SH2 and SH3 domains are commonly involved in non-catalytic regulatory properties. However, all three domains are essential in signal transduction[8,90-94] (Figure 1D and E).

3.2. Src structure and regulatory mechanism

The primary function of the Src is to transmit the external signal to the cell interior by phosphorylating tyrosine residues on substrates, mainly downstream of RTKs and integrins.[95] Src kinases are crucial in various cellular processes, such as cell proliferation, adhesion, migration, and more.[42] The Src kinase's complicated regulation is due to its complex structure. The structures of SH3, SH2, and SH1 KDs of Src kinases have been extensively studied and reviewed elsewhere. The Src KD features a characteristic bilobed architecture comprising a small N-terminal lobe and a large C-terminal lobe. The residues 267–337 and 341–520 make up these lobes, respectively. The N-lobe predominantly anchors and orients ATP, featuring a G-rich loop, which is a part of the nucleotide-phosphate binding site. The N-lobe is mostly composed of antiparallel β-sheet structures.[96] The C-lobe is predominantly composed of α helix, responsible for binding the protein substrates and contributing to the ATP-binding site. The catalytic site of Src is situated in a cleft between these two lobes; they open and close during ATP hydrolysis.[97] The dynamic conformational switch regulates ATP binding and ADP release; the open form is required to allow ATP to its catalytic pocket and release ADP; the closed form is important to bring residues into the catalytically active form. The Src kinase regulation precisely involved the coordination of non-regulatory SH2 and SH3 domains and a regulatory KD.[89,97] In the autoinhibitory conformation, the SH2 domain binds to phosphotyrosine-containing motifs, precisely, phosphorylated Tyr527 in the C-terminal tail of Src and stabilizes the conformation.[89,97] The SH3 domain interacts with a polyproline-rich motif situated between the SH2 and KDs. This interaction positions SH2–SH3 domains as a compact structural unit, which further prevents the movement of the KD and, consequently, locks the Src in its inactive state. The activation loop (residues 404–418) conformations in the KD dictate the active and inactive state of the Src kinase. In the inactive Src kinase, the activation loop forms a short α-helix between N- and C-lobes, known as the A-loop helix.[89,97] As a result, the Tyr416 residue side chain is buried between the N- and C-lobes, and this conformational switch leads to the prevention of the formation of a salt bridge between Lys295 and Glu310 required for enzyme activity. The autophosphorylation of Tyr416 disrupts the autoinhibitory state of the Src kinase, leading to an extended conformational switch in the activation loop and alignment of catalytic residues such as Asp386 and Asp404. Asp386 residue acts as a catalytic base for the tyrosine substrate, whereas Asp404 interacts with magnesium ions that stabilize ATP. Numerous studies on Src have revealed that SH2 and SH3 domains are critical

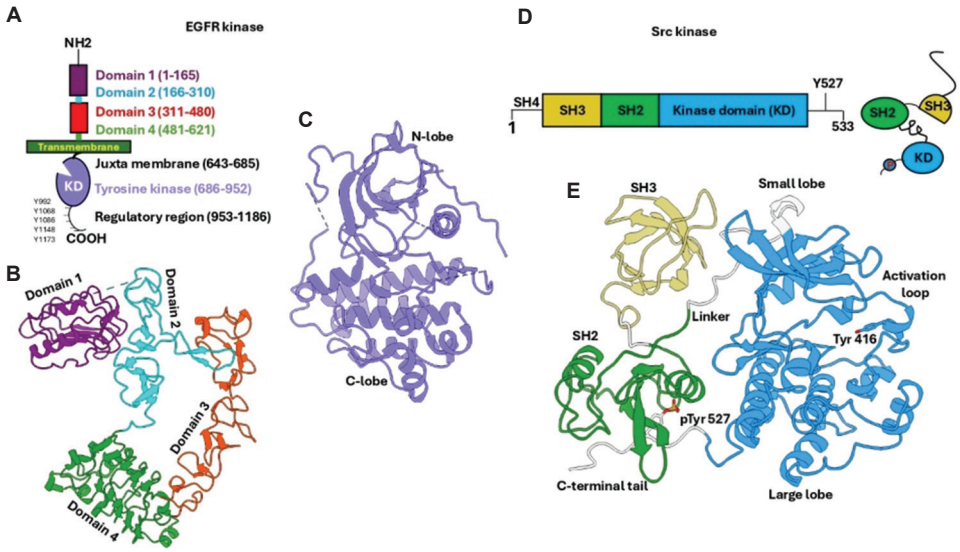

Figure 1. Structural architecture of EGFR and Src kinases. (A) The domain architecture of EGFR. (B) The extracellular region of EGFR is composed of four domains I–IV: domain I (red), domain II (cyan), domain III (green), and domain IV (orange) (PDB: 4KRP). (C) The EGFR kinase domain is displayed in medium purple (PDB: 4LQM). (D) The domain architecture of Src. The boundaries of domains are based on the chicken numbering system. (E) Ribbon diagram displaying the overall structure of Src (PDB: 2SRC). The SH3 (pale yellow) and SH2 (green) domains coordinate the linker and C-terminal tail regions, respectively. The kinase domain is colored in blue. Figures are generated using UCSF ChimeraX: tools for structure building and analysis.
Abbreviations: EGFR: Epidermal growth factor receptor; PDB: Protein Data Bank; SH3: Src homology 3; SH2: Src homology 2.

for maintaining the autoinhibited state of Src. However, the KD is involved in severe conformational changes to switch between active and inactive states. This structural equilibrium is disrupted when C-terminal Tyr527 is mutated. In the case of v-Src, a mutation at Tyr527 has been shown to impair the SH2-SH3 interaction between the KD and result in constitutive kinase activity.[4,89]

The Src protein-tyrosine phosphorylation levels are balanced by counteraction between CSK and protein-tyrosine phosphatases (PTPs). Okada and Nakagawa[98] were the first to demonstrate that CSK, a cytoplasmic PTK, controls the regulatory tyrosine phosphorylation in rat brains. They also highlighted its efficiency in phosphorylating Src at Tyr527, a key regulatory site for its activation. In contrast, PTPs such as PTPε and PTPε facilitate the dephosphorylation of phosphotyrosine 527 in the Src KD, thereby displacing it, leading to Src kinase activation (Figure 2A and B). Structural studies have revealed that the substrate recognition mechanism between Src and PTPs relies on the cysteine-dependent active site of PTPs and the phosphorylated tyrosine side chain of Src.[99] Recent findings have identified two additional key charge-charge interactions between rPTPε and phospho-Src beyond the active site interactions.[100] These biochemical and structural insights are extremely important for the development of novel therapeutic strategies for targeting kinases, particularly in cancer treatment.

3.3. EGFR structure and regulatory mechanism

EGFR regulates multiple functions involved in developmental, metabolic, and physiological processes.[101] When exposed to ligands like EGF, the EGFR binds to EGF, undergoing a conformational switch from an inactive monomer to an active dimer (Figure 2C). This conformational change leads to autophosphorylation of the receptor, which sequentially activates downstream signaling pathways to control cell proliferation and differentiation. EGFR, along with growth factor-α, amphiregulin, and other ligands, promotes either homodimerization of two EGFRs or heterodimerization of EGFR with other family members.[102] Upon activation of RTKs, there is a subsequent activation of the downstream Ras/mitogen-activated protein kinase pathway, the pI3K/Akt pathway, and transcription pathways.[103]

3.4. Extracellular structure of EGFR

The extracellular structural modules of all four EGFR members have been thoroughly studied both in the presence and absence of their respective ligands, as well as in complexes with antibodies.[104,105] Atomic structures reveal two key conformations that are important in the extracellular modules. One is an extended form that facilitates the conformation of one protomer in the active dimer, while the other is folded over or tethered conformation where dimerization elements are buried. Upon ligand binding, the extracellular domains display

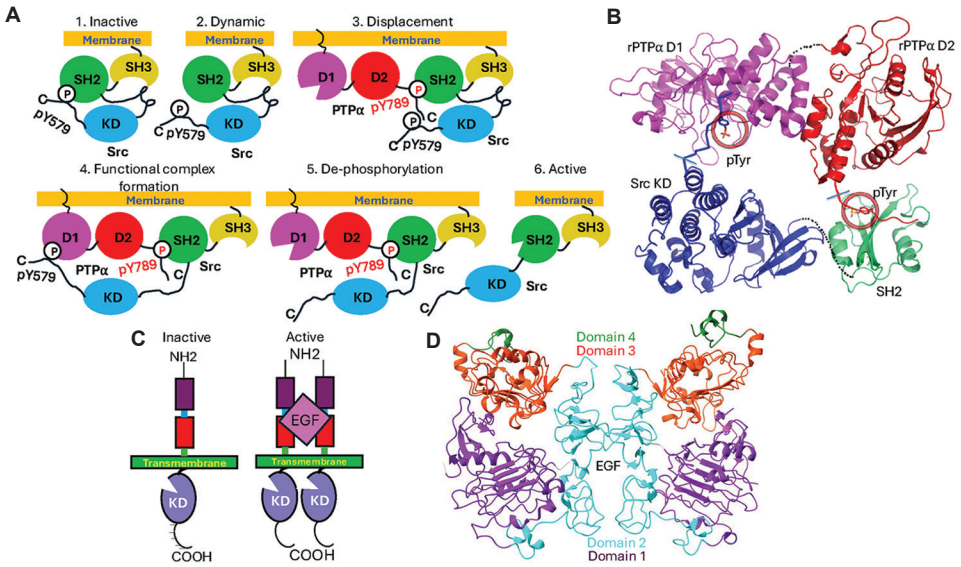

Figure 2. Structural transition of EGFR and activation mechanism of Src. (A). Schematic diagram of inactive EGFR, ligand-bound active dimeric extracellular EGFR, and an asymmetric dimer of kinase domain. (B) Structure of TGFα dimer of human EGFR (PDB ID: 1MOX). (C) Phosphotyrosine displacement by PTPα and activation mechanism of Src kinase.[99] (D) Haddock model of PTPα and Src kinase complex, displaying the phosphatase and tyrosine kinase interaction. Figures are generated using UCSF ChimeraX: tools for structure building and analysis.
Abbreviations: EFR: Epidermal growth factor; EGFR: Epidermal growth factor receptor; PTPα: Protein-tyrosine phosphatases; TGFα: Transforming growth factor alpha; PDB: Protein Data Bank; Src: Sarcoma.

a significant conformational change, transitioning the module from tethered to extended state, resulting in dimerization and activation of the EGFR (Figure 2D). This extended conformation is represented as a back-back dimer configuration, with the ligand positioned between domains I and III of each receptor subunit. The glycosylation of the EGFR extracellular region is critical for its activation; the sugar moiety around 40 kDa is known to play a role in EGFR maturation and cell-surface translocation. Mutation studies have identified that Asn579 is crucial for regulating receptor conformation and ligand binding affinity. Another mutation at Asn579, located on a specific glycosylation site, influences the structural conformation of EGFR and ligand binding. Furthermore, the N420D mutation in EGFR was shown to display ligand-independent activation through spontaneous oligomer formation.[105] Together, the biochemical and structural details underscore the complexity of these receptors' regulation and offer a base for therapeutic strategies targeting EGFR family members.

3.5. EGFR intracellular kinase structure activation

The intracellular region of EGFR mostly comprises its KD, which adopts a canonical kinase fold that exists in both active and inactive conformations. EGFR structure (unphosphorylated) in the presence of erlotinib from Genentech is the first atomic structure of the EGFR KD; this structure provides its unique structural features and activation mechanism.[103,106] The structure features the conserved Asp-Phe-Gly (DFG) motif at the base of the activation loop, which is a key activation/regulatory motif. In inactive conformation, the aspartic acid residue flips out of the catalytic center, making the kinase inactive and preventing the entry of ATP; this is observed in several kinases.[106] In the EGFR: erlotinib complex, the DFG motif is found in the 'in' conformation; in this, the activation loop is open and properly configured to bind its ligands. In addition, the active site element αC in the N-lobe switches inward and facilitates the ion pair interaction between Glu738 and Lys721, which is critical for catalytic activity.[105] In contrast to other kinases, EGFR does not require phosphorylation of its activation loop to transition to the active state. The atomic structure of EGFR in complex with lapatinib is captured in its inactive state; surprisingly, this structure resembles the inactive states of Src-family kinases.[105] In the structure, the αC-helix in the N-lobe switched outwards, and the activation loop formed a short helix, blocking its ATP binding. Mutations in the activation loop phosphorylation sites revealed that the phosphorylation is not an absolute requirement for EGFR's activation. Overall, the atomic details of these structures detailed the understanding of EGFR's regulatory flexibility and underlined its divergence from other RTKs, which rely on autoinhibitory interactions and activation loop phosphorylation for regulation.[105]

The activation mechanism of EGFR was revealed through the determination of the homodimer KD structure

determination. In this structure, one KD (activator) allosterically interacts with its partner (receiver) to activate the EGFR. This dimerization interaction occurs at the N-lobe of the receiver and the C-lobe of the activator, resembling the cyclin-mediated CDK type of activation. Unlike other RTKs, the EGFR activation mechanism is driven by protein-protein interactions at the dimerization interface. This mechanism is also observed in other members such as HER2, HER3, and HER4 (Figure 2A and B).[107] Further molecular dynamics simulation studies demonstrated how EGFR transitions between active and inactive conformations through local unfolding at the hinge region between N- and C-lobes. Together, these structural insights have significant clinical implications, helping in developing novel targeted antibodies like erlotinib and lapatinib, which exploit EGFR's conformational flexibility. For example, EGFR inhibitor Mig6 is known to block the asymmetric dimer interface and inhibit activation.[108] This understanding highlights the unique regulatory mechanism of EGFR and its critical role in cancer biology.

4. The role of TKs in cancers

TKs, a large family of kinases that include both RTKs and NRTKs, serve as critical molecular switches in regulating various cellular processes such as growth, survival, development, and differentiation.[83] Several studies have highlighted the role of PTKs in various cancers and their potential for drug discovery. The current review focuses on EGFR and Src's role as therapeutic targets for developing treatments against cancer cell-specific pathways.

4.1. Role of EFGR-tyrosine kinase in cancers

The EGFR family regulates developmental, metabolic, and physiological processes.[101] A key aspect of EGFR-driven cancers involves mutations in the tyrosine KD of the *EGFR* gene (exon 18–21), categorized into three classes: class I (in-frame deletions in exon 19), class II (single-nucleotide substitutions), and class III (in-frame duplications and or insertions in exon 20).[109,110] Class I accounts for approximately 44% of the activating EGFR-TK domain mutations, including deletion at LRE (Leu-747 to Glu-749), while class II mutations contribute ~41%, often affecting the KD C-helix. Class III mutations, constituting ~5%, are less frequent but still play a role in tumor progression.[103,111] Sigismund *et al.,* in 2018, best characterized the function of EGFR in ligand-and kinase-dependent activation, also known as the canonical EGFR signaling pathway.[112] Several of these stress pathways are activated in cancer cells to induce survival advantage as well as resistance to cancer therapy.[113,114] Casanova *et al.*[115] demonstrated that EGFR signaling is responsible for the Ha-ras-dependent activation in epidermal tumor cells. Recent publications support the activation of EGFR signaling pathways in epithelial cancers, including breast, ovarian, prostate, and non-small cell lung cancer (NSCLC).[116-118]

4.2. Role of Src-tyrosine kinase in cancers

SFKs play a crucial role in various cellular processes, such as cell proliferation, adhesion, and migration.[42] Their dysregulation is frequently implicated in tumors, where they are often overexpressed due to their role in cell-cell adhesion.[119,120] Particularly, Src is involved in activating STAT transcription factors, promoting tumorigenesis, and influencing cytokine signaling in hematopoietic cells.[121] It also plays a significant role in regulating the RAS/RAF/MEK/ERK MAPK and VEGF pathways in various tumors.[122] In addition, Src plays a vital role in facilitating tumor cell invasion by phosphorylating target substrates, aiding in the translocation of tumor cells through matrix barriers and tissue compartments. Invasion is a complex process, and tumor Src activation leads to the phosphorylation of targeted substrates, influencing the activity of cellular proteins to carry out this entire cellular process.[123] SFKs are activated in tumors through mutations of the Src allele, leading to a disorganized negative regulatory pathway or by binding to activating partners such as growth factors (Her 2/Neu, PDGF, EGFR). Oncogenic Src (v-Src) can activate Ras by recruiting the Grd 2/Sos complex, thereby stimulating Ras-mediated tumorigenic signals.[124] Furthermore, p120RasGAP-mediated activation of c-Src is important for Ras-induced tumor invasion.[125] The TME plays a crucial role in Src upregulation, leading to enhanced Src activity during cancer progression.[126] In addition, inhibitory phosphorylation of Tyr530 is mediated by the kinase Csk, which acts as a crucial regulator of Src activity.[127] Given the importance of Src/EGFR in tumor progression, the review will explore tyrosine kinase therapeutic targets and also provide insights into potential strategies for overcoming therapeutic resistance.

5. TKs as therapeutic targets

5.1. Development of TKIs

Cancer cell survival in the TME is challenging and highly influenced by external factors. Cancer treatment has advanced in developing TKIs. Discovery and development of imatinib (Gleevec, Inc.,) as the first effective TKI to treat chronic myeloid leukemia established it as a tumor-targeted therapy that acts specifically against the BCR-ABL fusion protein. Inhibitors such as sorafenib and sunitinib served as early examples of TKIs approved for solid tumors and renal cell carcinoma.[128] Over the past 20 years, robust and specific TKIs with single or multiple targets have been identified, including EGFR, ROS1, VEGFR, MEK,

Table 3. Tyrosine kinase inhibitors used in research

TKIs in EGFRm NSCLC (clinical and research data)	TKI	Clinical phase	Number of patients (%EGFRm+)	Response rate (%)
First/Second-generation EGFR TKI	Neratinib[132]	II	91 (100)	3
	XL647[133]	II	33 (53)	3
	Afatinib (A) vs. placebo (P)[134]	IIB/III	585 (16)	7 (A) < 1 (P)
	Afatinib[135]	II	62 (73)	8
	Dacomitinib[136]	II	62 (73)	8
	MM-121 + erlotinib[137]	II	50 (48)	9
	AP26113[138]	I	32 (35)	3a
Mutant-specific TKI	CO-1686[139]	I	40 T790M+ (100)	58
	AZD9291[140]	I	107 T790M+ (100)	64
	HM61713[141]	I	48 T790M+ (100)	29
EGFR antibodies	Cetuximab + erlotinib[142]	II	19 (84)	0
	Cetuximab + afatinib[143]	IB	126 (98)	29
Chemotherapy	Carboplatin/paclitaxel	III	52 (100)	28.8
	CE vs. C[144]	Retro	78 (100)	41 (CE); 18 (C)
	Pemetrexed + gefitinib or erlotinib[145]	II	27 (100)	25.9

Abbreviations: EGFR: Epidermal growth factor receptor; EGFRm+: Epidermal growth factor receptor mutation-positive; TKI: Tyrosine kinase inhibitor; CE: Chemo/erlotinib; C: Chemo.

FGFR, and PDGFR.[129] The known approved TKI is listed in Tables 3-5. IRIS trials (2000–2001) confirmed the long-term survival benefit of treating imatinib.[130] However, there has been concern over the emergence of resistance to imatinib. Nilotinib and dasatinib are two of the TKIs (second-generation) approved worldwide for the treatment of chronic myeloid leukemia after imatinib failure.[130] Developing TKIs is always a challenging endeavor because most patients develop acquired resistance against TKIs within a median period of 10–15 months.[131]

Two main approaches to therapeutically targeting EGFR rely on using mAbs and small molecules of EGFR-TKIs. Monoclonal antibodies (mAbs) specific to EGFR target the extracellular domain, whereas EGFR-TKIs block the binding of ATP to the intracellular catalytic domain of EGFR.[149] For example, panitumumab and cetuximab are two approved mAbs widely used in the treatment of colorectal cancer patients whose tumors express wild-type kirsten rat sarcoma viral oncogene homolog (KRAS), as KRAS mutations are associated with resistance to anti-EGFR therapies.[150] Erlotinib and gefitinib are two selective TKIs used in combination with mAbs in the treatment of NSCLC. Several preclinical and clinical studies were conducted to study the effect of these EGFR inhibitors alone and in combination with mAbs/chemotherapies.[151] Cetuximab and panitumumab have been studied in combination with anthracycline/taxane-based chemotherapy through pilot multicentric studies of neoadjuvant triple-negative breast cancers (TNBC).[152] Studies reported that using cetuximab in combination with either gefitinib or erlotinib has proven to enhance apoptosis and growth inhibition of neck cancer cell lines over using them alone in the treatment.[153] In addition, it is suggested that cetuximab and gefitinib showed a synergistic effect on EGFR downstream signaling pathways.[154] Trastuzumab, in combination with lapatinib, is used to treat HER2-overexpressed breast cancer; these two develop resistance in patients when treated alone.[155] One of the strong reasons to use combinational therapy including mAbs and selective EGFR-TKIs was to target different molecular domains of the EGFR. However, selective targeting of EGFR was limited to EGFR-driven cancers; in the case of EGFR- and KRAS- or STKs-driven cancers, one needs to be more selective in choosing combinational therapies.

6. Resistance to TKIs and strategies to overcome resistance

TKIs are the most common and successful strategies for targeting cancer cells.[156] However, eventually, cancer cells develop resistance to these drugs. Multi-drug resistance

Table 4. U.S. FDA-approved tyrosine kinase inhibitors for use in cancer therapy[146,147]

TKI	Family targeted	Inhibitor name	Application	Adverse effects (cardio-related)	Extra-cardio adverse effects
First-generation TKI	EGFR/ERBB family	Gefitinib	NSCLC	MI	Skin rashes, nausea, diarrhea, anorexia, stomatitis, nausea
First-generation TKI	EGFR/ERBB family	Icotinib	NSCLC	HTN	Diarrhea, nausea, skin rashes, loss of appetite
First-generation TKI	EGFR/ERBB family	Lapatinib	Breast cancer	HF, LVD	Skin rashes, diarrhea, nausea
First-generation TKI	EGFR/ERBB family	Erlotinib	NSCLC and prostate cancer	Edema	Skin rashes, diarrhea, nausea, loss of appetite, fatigue, neuropathy, alopecia
Second-generation TKI	EGFR/ERBB family	Afatinib	NSCLC	HTN	Severe diarrhea, loss of appetite, paronychia, dry skin, rashes
Second-generation TKI	EGFR/ERBB family	Neratinib	Breast cancer	Low rates and decline in LVEF and QT prolongation	GI-related disorders, headache, fatigue, diarrhea
Second-generation TKI	EGFR/ERBB family	Dacomitinib	EGFR-mutated NSCLC	HTN	Dry skin, appetite loss, diarrhea, weight loss, alopecia, cough, hemorrhoids, wounds, back pain, headache
Third-generation TKI	EGFR/ERBB family	Osimertinib	NSCLC	MI, pericardial effusion, LVD, HF	Diarrhea, nausea, fatigue, stomatitis
Third-generation TKI	EGFR/ERBB family	Pyrotinib	HER2-postive	-	Diarrhea, hand-foot syndrome, leukopenia, neutropenia, GI disorders, increased ALT, anemia, asthenia
Third-generation TKI	EGFR/ERBB family	Mobocertinib	EGFR-mutated NSCLC	-	Acneiform dermatitis, GI disorders, rash, dry skin, stomatitis, fatigue, rash, paronychia, anemia

Abbreviations: ALT: Alanine transaminase; EGFR: Epidermal growth factor receptor; FDA: Food and Drug Administration; GI: Gastrointestinal; HER: Human epidermal growth factor receptor; HF: Heart failure; HTN: Hypertension; LVD: Left ventricular dysfunction; NSCLC: Non-small cell lung cancer; MI: Myocardial infarction; TKI: Tyrosine kinase inhibitor; ERBB: Erythroblastic leukemia viral oncogene homolog.

in cancer arises when tumors become nonresponsive to chemotherapeutic agents. Many factors contribute to multi-drug resistance, including enhanced drug efflux caused by overexpressed ABC transporters,[157] genetic mutations, the activation of specific signaling pathways, and intracellular-extracellular ATP.[158] Mutations in the EGFR and Src also contribute to drug resistance in cancers. To overcome multi-drug resistance, researchers have developed strategies emphasizing the use of mAbs that target specific receptors or signaling components of the pathway, or any protein that specifically promotes tumor oncogenesis. Here, we highlight the use of mAbs alone and in combination to achieve effective treatment against cancers.

Resistance to TKIs in *EGFR*-mutated NSCLC remains a challenge in cancer therapy. Studies have identified that, on average, 50% of resistance to first- and second-generation EGFR-TKIs is due to the EGFR T790M mutation. This amino acid substitution in EGFR leads to an increased affinity to ATP caused by a conformational change, resulting in steric hindrance and reducing drug efficacy.[159] Osimertinib, a third-generation EGFR-TKI, inhibits both EGFR T790M and EGFR-sensitizing mutations, demonstrating increased efficiency over gefitinib and erlotinib.[160] However, patients developed resistance to long-term usage of third-generation EGFR-TKIs, particularly EGFR C797S on exon 20, as the main cause for this acquired resistance.[161] Patients responded to a combination of first- and third-generation EGFR-TKIs when harboring C797S in trans with T790M, whereas those with C797S in cis with T790M did not respond to this combination.[162] EGFR T790 and Src-mediated resistance are two distinct mechanisms where tumor cells develop resistance to therapies, especially EGFR-targeted therapies. Most of the TKIs that target EGFR were less sensitive because of the specific mutation in the *EGFR* gene, whereas Src-mediated resistance involves the activation of Src kinase, which can also bypass the effects of EGFR inhibitors and drugs that target NTKIs.[163] To overcome this evolving resistance, researchers are developing fourth-generation

Table 5. List of approved monoclonal antibodies targeting EGFR[148]

mAbs	Nature of molecule	Binds to	Antibody-dependent cell-mediated cytotoxicity	Mechanism	Clinical approval
Nimotuzumab	Humanized, mouse mAb	Extracellular domain of EGFR	-	Prevents binding of EGF	Yes, phase III (approved for treating HNSCC in non-USA countries)
Zalutumumab	Humanized IgG1	Extracellular domain of EGFR	Yes	Prevents the binding of ligands such as EGF and TGFα, thereby inhibiting EGFR signaling	Yes, phase III
Trastuzumab	Humanized IgG1	Juxtamembrane domain IV	Yes	Inhibits HER2 homodimers and ligand-independent HER2–HER3 dimers	Yes
Pertuzumab	Humanized IgG1	Heterodimerization domain II	Yes	Inhibits ligand-induced HER2-containing heterodimers	Yes
Cetuximab	Humanized IgG1	Extracellular domain of EGFR	Yes	Prevents the binding of ligands like EGF and TGFα, thereby inhibiting EGFR signaling	Yes
Panitumumab	Humanized IgG1	Extracellular domain of EGFR	Yes	Prevents the binding of ligands such as EGF and TGFα, thereby inhibiting EGFR signaling	Yes, phase III

Abbreviations: EGF: Epidermal growth factor; EGFR: Epidermal growth factor receptor; HER: Human epidermal growth factor receptor; HNSCC: Head-and-neck squamous cell carcinoma; mAb: Monoclonal antibody; NSCLC: Non-small cell lung cancer; TGFα: Transforming growth factor alpha; IgG1: Immunoglobulin G1.

EGFR-TKIs and also exploring combination therapies. For instance, EGFR-TKIs combined with programmed death ligand 1 antibodies with chemotherapy have shown significant survival benefits to patients suffering from *EGFR* mutation-driven drug resistance in cancers.[164] The FDA-approved TKI and NTKI inhibitors used in cancer therapy are listed in Tables 3 and 4.

7. Resistance and the mechanism of developing resistance to therapy

Trastuzumab (Herceptin), a therapeutic antibody used to treat breast cancer, often encounters resistance in patients. It binds to an epitope in the juxtamembrane region of the HER2 RTKs. Upon binding, trastuzumab induces uncoupling of ligand-independent HER2-HER3 heterodimers and inhibits downstream signaling as well as antibody-dependent cell cytotoxicity.[165] The main reasons reported for resistance to trastuzumab in patients are decreased interactions with HER2 due to blockage by cell-surface proteins like mucin-4.[166] Consistent treatment with trastuzumab leads to decreased expression of the tumor suppressor *PTEN* gene and activation of the Akt signaling pathway. Another main reason for developing resistance is the activation of the phosphatidylinositol 3-kinase/Akt pathway, which can lead to decreased sensitivity to trastuzumab.[167] Another potential explanation for the development of trastuzumab resistance is its ability to bind to hyaluronan and CD44, a transmembrane receptor that can hinder trastuzumab's access to HER2.[168] A clinical study was conducted to analyze sensitivity to trastuzumab treatment and reported in the study on 46 patients with breast cancer, in which 11.1% of patients responded to trastuzumab (expressing p95HER2), with 51.4% of the patients who expressed p185HER2 achieving clinical response.[169] Lapatinib, a small molecule that can inhibit both HER2 and EGFR kinase, was tested in p95HER2 preclinical studies to prevent HER2 signaling loss of the trastuzumab binding site.[169] Coupled lapatinib with trastuzumab has been clinically shown to be effective in patients with stage IV HER-overexpressing breast cancer.[170]

Cetuximab is an mAb that treats metastatic colorectal cancer and squamous cell cancer (head-and-neck squamous cell cancer). The use of cetuximab and panitumumab in colorectal cancer patients is successful.[171,172] However, treatment with cetuximab and panitumumab as single agents was only 10% effective in clinical significance. This clearly explains the development of resistance to the therapy. Most patients develop resistance within 3–12 months of starting therapy.[173] The most probable explanation for developing resistance is, but not limited to, *RAS* mutations

(these mutations prevent patients from having a response to therapy). Acquired resistance is another important reason when using EGFR-targeted mAbs. Preclinical and molecular profiling of clinical specimens that developed resistance to EGFR-targeted mAbs have revealed genetic alterations of genes in the EGFR-RAS-RAF-MEK signaling pathway, and RTKs are the mechanism of acquired resistance to anti-EGFR mAbs.[174-176] Mutations in codons 12 and 13 of *KRAS* were the first identified mechanism of primary resistance to anti-EGFR therapy; later, patients were screened for *KRAS* mutations before mAb treatment. Researchers also reported that oncogenic Ras and wild-type p53 stimulate STAT non-cell autonomously and promote tumor radioresistance.[122] However, in some instances, RAS wildtype patients can be non-responders to anti-EGFR therapy, as it is well understood that additional mechanisms of intrinsic resistance are attributed to mutations in PI3KCA/BRAF.[177,178] The above genetic mutations leading to acquired resistance and escape from anti-EGFR blockade appear to converge on the activation of MEK-ERK/AKT signaling pathways. Considering that each mAb has distinct advantages and disadvantages in therapy, treatment selection should be guided by the molecular profile of the tumor and the patient's clinical context.

Pertuzumab (Omnitarg, 2C4) is an anti-HER2 mAb that binds to the domain II epitope of HER2 and is able to block a binding pocket essential for receptor dimerization and signaling. Pertuzumab is speculated to engage in a potential synergism with trastuzumab in HER2-overexpressing cell lines. Phase II clinical trials of pertuzumab in combination with trastuzumab have shown disease progression over trastuzumab in patients with HER2-overexpressing metastatic breast cancer.[179] Currently, clinical trials in different stages testing pertuzumab in combination with trastuzumab in different settings and as well as pertuzumab with chemotherapy, are ongoing.[180] Toxicity profiles of these new antibodies are comparable to that of cetuximab, even though they are associated with less hypersensitivity reactions. Mostly, mAbs administrations needed frequent clinical visits due to their mode of administration (intravenous infusions). Also, the proposed resistance to cetuximab can be applied to most EGFR-targeted mAbs. From these studies, it is well understood that mAbs targeting specific signaling molecules or receptors, in combination with other mAbs or chemotherapy, have shown progress in overcoming resistance in cancers.

7.1. Emerging strategies to enhance TKI efficacy

To further expand therapeutic options for overcoming resistance to mABs and TKIs, novel strategies such as antibody-drug conjugates (ADCs) and bispecific antibodies have emerged as promising alternatives that can deliver toxic payloads directly to tumor cells, potentially bypassing resistance mechanisms. Specifically, ADCs are designed to target cells expressing specific cancer antigens, thus releasing the cytotoxic chemotherapeutic payload while sparing normal tissues. For example, trastuzumab deruxtecan (T-DXd), an ADC that is an approved treatment for metastatic HER2+breast cancer, can be used even in those resistant to traditional HER-2 targeted therapies[181] (Figure 3). Likewise, the bispecific T cell engager (BiTE) is an alternative and promising approach, combining tumor-associated antigens (such as EGFR or HER2) with CD3 on T cells to initiate immune-mediated tumor cell killing (Figure 3). Nevertheless, major mechanisms of resistance to BiTE therapy involve antigen loss and immunosuppressive factors such as immune checkpoint upregulation. Thus, next-generation immunotherapies may be required to enhance treatment effectiveness and reduce toxicity, especially for solid tumors where responses to BiTE therapy are consistently poor.[182] However, both ADCs and bispecific antibody therapies are not without limitations, causing side effects such as interstitial lung disease (in the case of T-DXd) and cytokine release syndrome with BiTEs. Despite these major challenges, the current advancements and alterations of such molecules highlight the dynamic and adaptive nature of cancer therapy, with continued focus on overcoming drug resistance and maximizing patient benefit.

8. Combined targeting EGFR and Src as a potential therapeutic approach

TNBC is an aggressive subtype of breast cancer with limited therapeutic options. It is characterized by the absence of estrogen and progesterone receptors and a lack of EGFR2 (HER2) gene amplification and protein expression.[183] Notably, overexpression of EGFR is highlighted in TNBC, attracting significant research interest in evaluating EGFR-TKIs as potential treatments.[184] Despite overexpression of EGFR in TNBC, the EGFR-specific TKIs have shown limited efficacy due to their intrinsic or acquired resistance mechanisms.[185] Studies identified the association of SFKs as a key factor that contributes to EGFR resistance, which has been shown to increase HER-family receptor expression.[186,187] The overexpression of Src enhances HER2/HER3 dimerization, consequently delaying receptor internalization and hence prolonging its downstream oncogenic signaling.[188-190] This crosstalk between EGFR and Src kinases suggests that targeting EGFR alone may not be sufficient, suggesting a dual-targeted approach that can inhibit Src signaling.

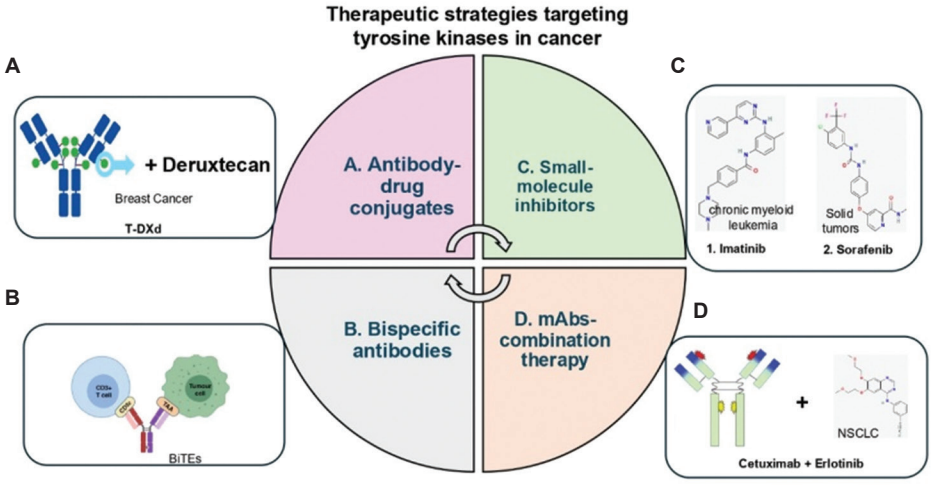

Figure 3. (A-D) Schematic illustrating the specific therapeutic strategies targeting tyrosine kinases in cancer. Image created by the authors. Abbreviations: BiTEs: Bispecific T cell engagers; mAbs: Monoclonal antibodies; NSCLC: Non-small cell lung cancer; T-DXd: Trastuzumab deruxtecan.

Dasatinib, an Src inhibitor, initially exhibits sensitivity in TNBC cells; however, resistance develops over time.[191,192] However, combining both EGFR and Src inhibitors has shown promising results.[193] For instance, afatinib (an irreversible pan-HER inhibitor) and Src inhibitors have shown synergistic effects in MDA-MB-468, TNBC cell lines. In addition, the combination of afatinib and dasatinib has also been shown to enhance apoptosis and growth suppression of NSCLC *in vitro* and *in vivo*.[194,195]

These preclinical research studies have progressed to phase I clinical trials evaluating the efficacy of these combination therapies (ClinicalTrials.gov identifier: NCT01999985). The cooperative interactions between these Src-TKs and HER family members in acquired resistance reveal the significance of developing novel combination drug therapies targeting both pathways. This combination of therapies may hold significant potential in overcoming multidrug resistance, improving treatment response, and increasing clinical benefits in TNBC and other EGFR-driven cancers.

8.1. Therapeutic challenges and limitations

The development of TKIs against cancer has significantly advanced in recent years. However, their clinical utility is often reduced by the extra-cardio adverse effects due to toxicity. It is well documented that older generations of TKIs can cause a wide range of cardiovascular issues such as hypertension, atrial fibrillation, and heart failure. These adverse effects highlight a critical therapeutic challenge: the necessity to design novel TKIs that maintain therapeutic efficacy with reduced off-target toxicities.[196] In addition to TKI toxicity, another limitation is the development of drug resistance, accompanied by postmenopausal symptoms, muscle/joint pains, and osteoporosis as common issues in prolonged usage of TKI therapy.[196] Both drug toxicity and the development of drug resistance attributed to long-term treatment necessitate the development of novel TKIs that strike a balance between specific target inhibition and favorable safety profiles. In general, the therapeutic design must prioritize both efficacy and reduction of toxicity to improve patient outcomes and long-term treatment sustainability.

9. Summary and conclusion

The current review highlights the crucial role of PTKs, with special emphasis on EGFR and Src, in regulating important cellular processes such as growth, differentiation, survival, and regulation underlying carcinogenesis. Furthermore, this review addresses the structural mechanism of EGFR and Src kinases that provides valuable insights into designing novel cancer therapies. Besides that, this review emphasizes the development of TKIs, including gefitinib and erlotinib, and the challenges posed by resistance in cancer treatment. We also outline and evaluate the existing clinical trials of combination therapy targeting EGFR and Src kinases, particularly in aggressive cancers like TNBC. In conclusion, EGFR and Src kinases are significant players in tumor development and therapeutic resistance. Hence, the development of inhibitors/combination treatment holds substantial promise in overcoming multidrug resistance and augmenting therapeutic response in a broad spectrum of cancers.

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Availability of data

The HADDOCK-generated Src: PTPα complex model shown in the review is available from the corresponding authors on request.

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