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Review Article

The ErbB Receptors and Associated Key Signalling Proteins in Cancer

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ABSTRACT

Cancer is a disease of almost all multicellular organisms, in which communication between cells plays a crucial role in the life and development of that organism. The ErbB family of tyrosine kinase receptors plays a fundamental part in signal transmission, controlling cell proliferation and survival. Signalling outputs of the ErbB receptors are tightly controlled under normal physiological conditions. However, genomic amplification, overexpression or mutational activation of these receptors and their signalling proteins is a common cause of cancer. This narrative review provides an overview of the structure, activation, and modes by which these receptors are dysregulated in oncogenesis. The critical downstream signalling pathways of RAS/RAF/MEK/ERK governing proliferation and PI3K/AKT/mTOR controlling survival are detailed. We discuss the development of ErbB-targeted therapies with emphasis on monoclonal antibodies and tyrosine kinase inhibitors and address the major challenge of therapy resistance. Next-generation tyrosine kinase inhibitors and combination therapies aimed at overcoming treatment failures are also outlined.

Introduction

Protein kinases, totaling 518 in humans, are important enzymes that have a key regulatory function in virtually all aspects of cell biology [1]. Tyrosine kinases are a distinct subgroup of 90 of these protein kinases and generally fall into two categories: receptor tyrosine kinases or non-receptor tyrosine kinases. There are 58 known members of receptor tyrosine kinases (RTKs) in humans that are grouped into 20 subfamilies sharing the same general structure [2]. They consist of an (amino group) N-terminal, an extracellular domain for binding ligands, a single transmembrane helix, a juxtamembrane regulatory region, an intracellular tyrosine kinase domain, and a (carboxyl group) C-terminal as depicted in Figure 1 [3]. The ErbB (Erythroblastic B named after the gene they originate from) receptors fall in one subfamily and are widely expressed throughout many cells [4]. While in normal tissues the ErbB receptors count typically does not exceed 100,000 per cell, their expression in cancer can exceed 2 million per cell, promoting uncontrolled cell proliferation [5]. There are four members in the ErbB subfamily of RTKs, and they are: 1) ErbB1 (also known as HER1 or EGFR), 2) ErbB2 (also known as HER2 or Neu), 3) ErbB3 (also known as HER3) and ErbB4 (also known as HER4). The ErbB receptors play a crucial role in cell growth, survival and differentiation and are often implicated in the development of cancer. The loss of ErbB receptors in mice results in organ defects in the heart, lung, brain, epidermis, and mammary glands emphasizing their essential roles in development [6,7]. In contrast, the overexpression of ErbB receptors in transgenic mice models showed the development and progression of many types of solid tumours [8].

The ErbB receptor-ligands are essentially divided into three groups based on their specificity to a particular receptor. Group 1 includes ligands which bind specifically to ErbB1 (EGFR) like epidermal growth factor (EGF), transforming growth factor alpha (TGF-α), amphiregulin (AR), and epigen (EPG). Group 2 ligands such as beta-cellulin (BTC), heparin-binding EGF (HB-EGF), and epiregulin (EPR) with dual specificity in binding to both ErbB1 and ErbB4. The third group of ligands include the neuroregulins 1,2,3, and 4 (NRG1, NRG2, NRG3 and NRG4) with NRG1 and NRG2 binding to ErbB3 and ErbB4 while NRG3 and NRG4 can only bind to ErbB4 [9-11]. No known ligand binds to ErbB2, which is termed the orphan receptor.

The ErbB receptors are usually expressed in epithelial, mesenchymal, and neuronal cells [12]. Under normal physiological conditions, the ErbB receptors are activated by the spatial and temporal expression of their ligands [13]. Ligand binding to the ectodomain of the receptor causes allosteric transition leading to receptor dimerization and the auto-transphosphorylation of tyrosine residues of the kinase domain and the cytoplasmic part of the receptor [14]. Moreover, receptor ErbB3, which is characterised by its impaired kinase activity, displays several tyrosine phosphorylation sites that can provide binding sites for signalling proteins [15]. Receptor dimerization and auto-transphosphorylation initiates signalling cascades to activate various effector proteins to perform the desired function of a particular pathway. Many of the roles of the effector proteins are implicated in mechanisms leading up to the development of cancer [16-18].

The RAS/RAF/MAPK and PI3K/AKT/mTOR signalling cascades have been extensively studied and their key components discovered. The ErbB-mediated signalling controls many of the cell functions required for growth, proliferation, and metastasis; hence, the overexpression of these receptors are often taken as a poor prognostic factor in cancer patients [19,20]. Mutations in these receptors and their signalling components were found to lead to aberrant signalling and cancer [21]. Gain-of-function mutations were found in approximately 30% of all solid tumours making some tumour cells so dependent on ErbB signalling that they display what is known as “oncogene addiction" [22]. However, this comes with a price in that singling out and targeting these receptors can often lead to therapy resistance.

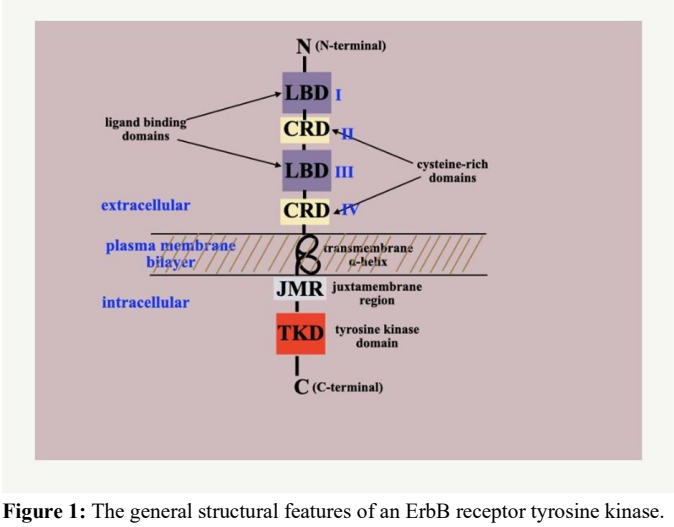

Figure 1: The general structural features of an ErbB receptor tyrosine kinase.

Structural features of the ErbB receptors

A common conserved feature of the ErbB receptors is the presence of an extracellular region, a transmembrane helix, and an intracellular part as depicted schematically in Figure 1. Small differences in the amino acids and their sequences exist between the four individual members of the ErbB receptors, reflecting variations in structure and function. The ErbB1 (EGFR) itself is a 170 kDa molecule spanning 1210 amino acids, and contains 28 exons, including the signalling peptide at its amino terminal [23]. The extracellular region, exons 1-16, consists of four domains numbered I to IV, with domains I and III characterised by being rich in the amino acid leucine, enabling interactions (dimerization) with an adjacent receptor, and domains II and IV being rich in the amino acid cysteine and are responsible for ligand binding 2,24. A simple conformational state is depicted in Figure 2, whereby domain II is folded towards domain IV, hindering domains II and IV from dimerization in the inactive state of the receptor. Ligand binding causes a substantial domain rearrangement to switch between the inactive state to the active conformation 2.

Due to the lack of ligand binding to ErbB2 receptor, it must function as a co-receptor through homodimerization or heterodimerizes with another ErbB partner 13,25. Additionally, ErbB2 exhibits a high level of constitutive, ligand-independent activity, causing it to drive tumour growth when its level of expression is above a certain threshold 10,13. The transmembrane (Tm) region is α-helical and composed of exon 17, which anchors the receptor into the cell membrane.

The intracellular region of ErbB receptors, comprising exons 18-28, contains a juxtamembrane regulatory sequence (JMR), a tyrosine kinase domain (TKD), and a carboxyl (C) terminal tail 26. The Juxtamembrane region is important in receptor activation and signal transduction and is involved in both dimerization and kinase activation 27. The TKD is crucial for the receptor trans-autophosphorylation and the activity of downstream signalling pathways 14. The kinase domain spans approximately 300 amino acids and has the characteristic bilobed structure seen in all protein kinases 2. The smaller lobe of TKD, the amino-terminal lobe, comprises five β-sheets and one α-helix, which primarily influences the overall conformation of the kinase domain. The larger loop, the carboxyl lobe, is mainly α-helical and is responsible for substrate binding. The two lobes are connected by a linker region and form a cleft where ATP binds 28,29. ATP binds in the cleft between the two lobes, and the tyrosine-containing sequence of the protein substrate interacts with the residues of the larger carboxyl lobe. The C-terminal tail of the receptors is rich in tyrosine residues, and their phosphorylation also facilitates downstream signalling cascades.

Activation of the ErbB receptors

Early studies on the activation of ErbB receptors revealed that two molecules of the ligands and two molecules of the receptors are involved in the activation of the receptors [30]. The activation of the ErbB receptors and the subsequent transmission of its signal can generally be divided into two steps: 1) ligand binding and dimerization, and 2) tyrosine kinase domain (TKD) activation 4. Processes involved in these two events are often hijacked by cancer.

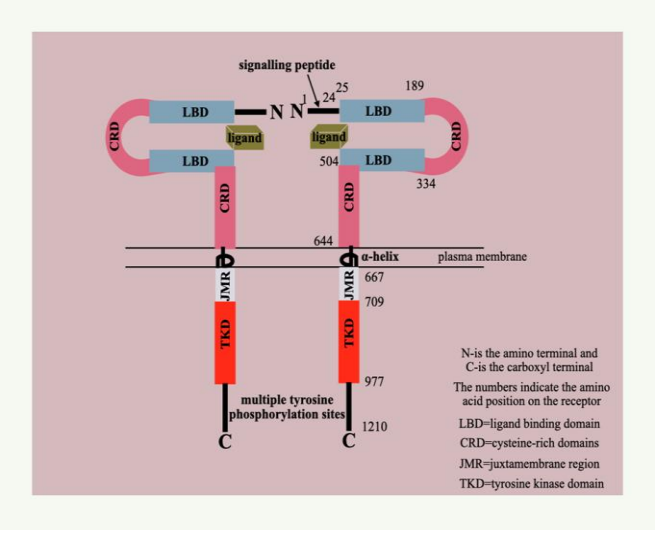

Figure 2: Dimerization of the ErbB receptors following ligand binding.

Ligand binding and dimerization

This event begins when a ligand, such as epidermal growth factor (EGF), binds to the extracellular ligand-binding domain (LBD) of a receptor monomer (domains I and III in Figure 3) [31,32]. Of note, ErbB2 does not have any recognised ligand to bind to; nevertheless, it is activated via heterodimerization with other ligand-bound receptors 10,33. Figure 3 shows that the two LBDs of the monomer receptor assume a conformational state that brings them close together to enable the sharing of one ligand. This ligand binding induces further conformational changes leading to the dimerization of two ErbB receptor molecules, forming either a homodimer (e.g., ErbB1-ErbB1) or a heterodimer (e.g., ErbB1-ErbB2) 4,10. The main contacts between the two receptors are the domains II of the partner molecules. A dimerization arm extends from domain II of one receptor to the adjacent partner's domain II, and vice versa. The deletion of, or mutations in, the dimerization arm confirmed the importance of this region of the receptor in the dimer formation [34,35].

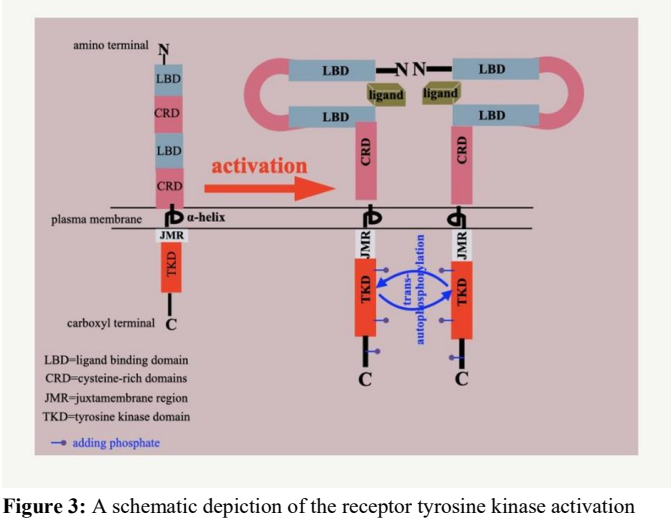

Figure 3: A schematic depiction of the receptor tyrosine kinase activation mechanism.

Tyrosine kinase domain (TKD) activation

The dimerization of the ErbB receptors brings their tyrosine kinase domains (TKDs), located within the intracellular cytoplasmic regions, near each other. This proximity will facilitate their activation through trans-autophosphorylation of several tyrosine residues on the partner monomer. The key event of auto-transphosphorylation marks a transition from a dormant "inactive" state to an "active" receptor kinase domain 3. Of note, ErbB3, due to its impaired kinase function, only acquires this signalling potential when it dimerizes with another member of the ErbB receptors with kinase activity [36]. The activated TKDs will also trans-autophosphorylate tyrosine residues on the receptor's intracellular tail, and these phosphorylated residues will act as docking sites for downstream signalling proteins. These phosphotyrosine sites recruit cytoplasmic signalling molecules such as the adaptor protein Grb2 containing the SH2 (Src homology 2) domain with a high affinity for phosphotyrosine residues [37-39]. One of the key proteins, activated by these phosphorylated tyrosine residues on the receptor C-terminal tail, is the rat sarcoma (RAS) protein which acts as a molecular switch that propagates the signal downstream. The RAS node is crucial to both signalling pathways, RAS/RAF/MAPK and RAS/PI3K/AKT/mTOR cascades, detailed below.

ErbB receptor signalling in cancer

Following the activation of ErbB receptors and the generation of phosphotyrosines on the C-terminal, various proteins containing SH2 (Src homology 2) or PTB (phosphotyrosine binding) domains are recruited to initiate downstream signalling cascades via various pathways 3,12,41,42. One crucial pathway is called the RAS/RAF/MAPK cascade. In this pathway, an adaptor protein called growth factor receptor binding protein 2 (Grb2) is recruited to bind directly to these phosphotyrosines (or indirectly through another adaptor protein called Shc) [42,43]. Figure 4 depicts the initiation of this signalling with the direct binding of Grb2 to phosphotyrosine. The Grb2 avidity to phosphotyrosines is facilitated by the presence of an SH2 domain in part of its structure. Moreover, Grb2 has another important domain called SH3 (Src homology 3), which is rich in proline amino acids. SH3, the proline-rich domain, of Grb2 attracts and activates another signalling molecule termed son of sevenless (SOS) to form a complex with the ErbB receptor. SOS will then detach from this complex and translocate to the membrane to activate the all-important signalling molecule, RAS (rat sarcoma) protein [42-44]. SOS activates RAS by binding to its guanine exchange factor (GEF) domain [45]. The RAS protein is a monomeric G protein attached to the underside of the phospholipid bilayer of the plasma membrane. RAS exists, as is normally the case with all G-proteins, in two states: an "OFF" GDP inactive state and an "ON" GTP active state. The binding of SOS to RAS causes the GDP of the latter to fall off and GTP from the cytoplasm to jump in to occupy the space. This turns the RAS protein from its inactive "OFF" state to an active "ON" configuration. SOS will then cleave away from RAS leaving it wandering around in the plasma membrane, whilst it is in the active state, to initiate the RAS signalling pathway 11.

The activated RAS protein recruits RAF protein kinase, to the inner side of the phospholipid bilayer of the plasma membrane and activates it through tyrosine phosphorylation 46. Subsequently, the activated RAF protein interacts and activates MEK kinase, which in turn activates downstream proteins, including ERK (extracellular ligand–regulated kinase) 43. ERK will then translocate to the nucleus to

stimulate various transcription factors that are involved in cell proliferation, differentiation, and migration 41,42,44.

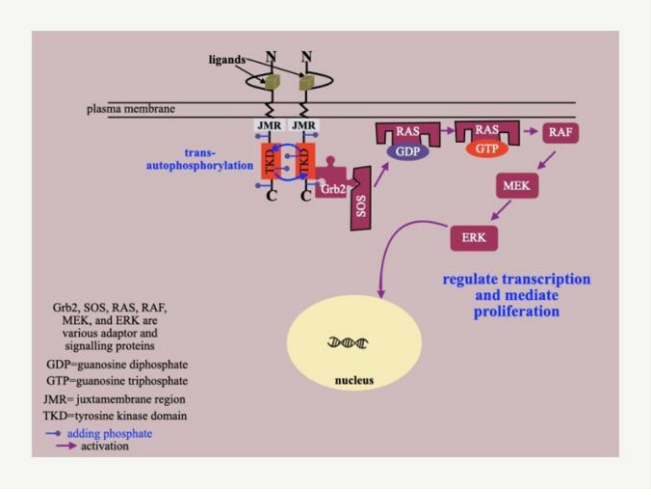

Figure 4: A summarized view of the RAS/RAF/MAPK signalling pathway of the ErbB receptors.

The other highly important ErbB receptor kinase signalling in relation to cancer is called the PI3K/AKT/mTOR cascade, as illustrated in Figure 5 47. Following the ErbB receptor activation and the phosphorylation of its tyrosine C-terminal tail, the activated receptor can directly recruit the PI3K protein. PI3K has two subunits: a regulatory subunit called p85 containing two SH2 domains, one located at its N-terminal and the other situated at its C-terminal, and a catalytic subunit called p110 48. The recruitment of PI3K protein to phosphotyrosines is facilitated by the two SH2 domains. The translocation of PI3K to be close to the tyrosine kinase domain of the ErbB receptor promotes its activation to catalyse the conversion of phosphatidylinositol (4,5) bisphosphate (PIP2) to phosphatidylinositol (3,4,5) trisphosphate (PIP3) at the underside of the cell membrane 11,47. It should also be noted that the activation of PI3K protein to convert PIP2 to PIP3 is also promoted by the presence of activated RAS nearby 49. The production of PIP3 yields good docking sites for various proteins with pleckstrin homology (PH) domain, and some of the prominent ones are: PDK1 and AKT (also called protein kinase B (PKB)) 47,48. PDK1 then phosphorylates AKT at the Thr308 (threonine number 308 in the amino acid sequence) site, while another kinase, often referred to as PDK2, phosphorylates AKT at the Ser473 (serine number 473) position 50. This dual phosphorylation of AKT is crucial for its full activation, detachment, and readiness to phosphorylate several cytoplasmic and nuclear proteins. Amongst one of its important cytoplasmic target proteins is mTORC1 (mammalian target of rapamycin complex 1). A key part of this complex is the threonine/serine kinase mTOR. Other accessory proteins forming mTORC1 are PRAS40 (proline-rich AKT substrate 40), DEPTOR (DEP domain-containing mTOR interacting protein), mlst8 (mammalian lethal with sec13 protein 8), and RAPTOR (regulatory associated protein of mTOR) 51. It is thought that both PRAS40 and DEPTOR exert a negative regulatory influence on mTORC1, and once mTOR is activated, it phosphorylates and loosens the hold on these two accessory proteins to act as a positive feedback loop. The main way AKT phosphorylates mTORC1 is through acting on a protein complex called TSC1 (hamartin)/TSC2 (tuberin) (tuberous sclerosis complex) 48. AKT inactivates this complex by phosphorylating the TSC2 component, causing it to leave the complex and associate with another partner protein called 14-3-3. When TSC1/TSC2 complex is in the active state it acts on the GTPase activity of a protein called Rheb, facilitating its conversion into Rheb-GDP, thereby inhibiting mTORC1. However, when TSC1/TSC2 complex is in the inactive state, having lost its partner dimer, the Rheb protein will not be deactivated and will remain in the Rheb-GTP state, and its relative amounts will build up in the cytoplasm to go and activate mTOR. The activated m-TOR will activate the translational machinery of the cell. Mammalian target of rapamycin is an evolutionarily conserved protein that is essential for life, and its embryonic mutations proved to be lethal 48.

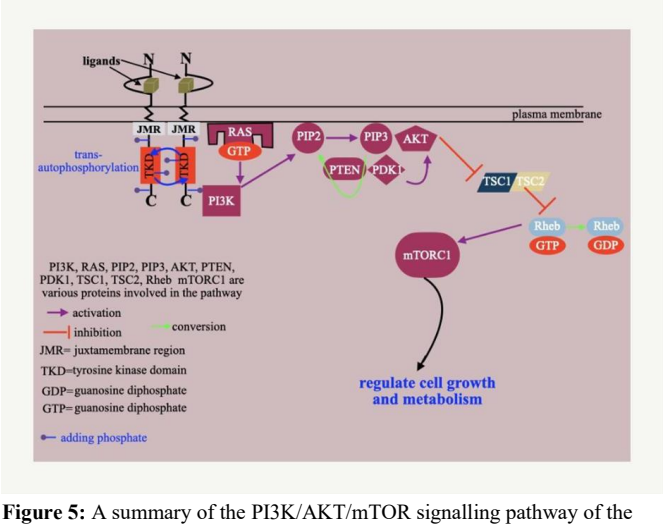

Figure 5: A summary of the PI3K/AKT/mTOR signalling pathway of the ErbB receptors

Dysregulated ErbB receptors and signalling in cancer

Physiological modulation of ErbB receptor activity is carried out by phosphatase enzymes, which serve to remove the phosphate groups and deactivate the receptors 39. Beyond that, the dysregulation of ErbB receptors can occur at the receptor level or at the downstream signalling cascades.

Receptor-level dysregulation

This is the most common cause of dysregulated ErbB receptors and often makes them good targets for cancer therapy 10,52. ErbB1 receptor is often overexpressed in head and neck cancer and in subsets of lung, colon, and ovarian cancers. The presence of multiple copies of the gene encoding ErbB2 is associated with 20% of breast cancer cases and is referred to as HER2-positive 53. ErbB2 is also overexpressed in subsets of other malignancies, such as gastric and ovarian cancers. Activating somatic mutations in the genes encoding ErbB receptors can cause the receptors to be permanently “on” despite the absence of binding ligands. Classic examples are the L858R (leucine 858 to arginine) point mutation in exon 21 and the deletion of exon 19 in the tyrosine kinase domain of ErbB1 receptor, leading to its constitutive activation 54. These two mutations are often referred to as the classical ErbB1 mutations and occur in about 85% of non-small cell lung cancer (NSCLC). A further example is the creation of EGFRvIII variant in glioblastoma, where ErbB1 suffers from a deletion of exons 2-7 in its extracellular domain rendering it unable to bind ligands. Despite this, EGFRvIII displays low-level

constitutive functioning, and its aberrant signalling was shown to be important in driving tumour progression and often correlates with poor prognosis 55.

Cancer cells themselves can start producing ligands that activate ErbB receptors and create a self-stimulatory "autocrine loop" that is commonly observed in glioblastoma and in NSCLC 36. Signalling of the ErbB receptors can be turned off through endocytosis and internalisation. Mutations in the gene CBL, which encodes a protein that functions as an E3 ubiquitin ligase, can prevent the degradation of ErbB receptors, causing them to signal for longer 56.

Downstream signalling dysregulation

Downstream signalling pathways can be hijacked despite the presence of normally functioning ErbB receptors. The primary proliferative pathway of RAS/RAF/MAPK can become independent of upstream signals through mutations in its key proteins, particularly members of the RAS family. KRAS mutations, for instance, are found in about 90% of pancreatic cancer, 45% of colorectal cancer, and in about 30% of lung cancers 57. A mutated KRAS gene that is permanently "on" can continuously send growth signals even in the absence of the ErbB1 receptor. The critical survival and growth pathway downstream of ErbB3, PI3K/AKT/mTOR, can be activated by the loss of tumour suppressor protein PTEN 58. This tumour suppressor acts through the conversion of PIP3 back into PIP2, as illustrated in Figure 5, and its loss causes hyperactivation of AKT signalling regardless of receptor status. Moreover, gain-of-function mutations in the catalytic subunit of PI3K are common in breast, colorectal, and other cancers 59.

Dysregulation of crosstalk signalling partners

As ErbB signalling does not normally operate in isolation from signals it receives from other pathways, it becomes obvious that malfunctioning in the partner's signals can also lead to the dysregulation of ErbB receptor signalling. For example, GPCRs can transactivate ErbB receptors through secondary messengers, and the integrin cell adhesion molecules can co-activate some ErbB receptors 60.

Targeting ErbB receptor signalling in cancer

Silencing ErbB receptor signalling in cancer is primarily concerned with blocking signal transmission to downstream effector proteins, i.e., inhibiting the receptors themselves rather than their associated signals. There are two main strategies involved in achieving this, together with more recent developments based on knowledge and experience gained from these studies (refer to Table 1) 61. The two major approaches are: 1) using monoclonal antibodies (mAbs) which target the ErbB ectodomains or antagonise interactions between ligands and receptor, and 2) using tyrosine kinase inhibitors (TKIs) which bind to the ATP-binding pockets located within the catalytic domain of the ErbB receptor. However, resistance to these therapies often develops, demanding novel improvements to overcome these mechanisms. Below, we are mainly focusing on regulatory-approved therapies, although there is a plethora of other treatments under preclinical evaluation or going through clinical trials and assessment.

Monoclonal antibodies (mAbs)

These are large proteins that are designed to target the extracellular region of ErbB receptors. They achieve this function through 1) blocking the binding of the ligands to the receptor thus inhibiting its activation, 2) triggering degradation and internalisation of the receptor by binding to it so rendering it unavailable for signalling, 3) recruiting immune cells such as natural killer cells to attack and eliminate the antibody-bound cancer cells and 4) inhibiting the critical step of receptor dimerization thus deactivating subsequent steps in the overall signalling process 20,62,63. Previous research focused on targeting ErbB1 and ErbB2, although there have been recent efforts evaluating the value of ErbB3 64. Four mAbs have so far been approved by the European Medicines agency (EMA) and the US Food and Drug administration (FDA) for clinical use against ErbB1, and these are: Cetuximab, Panitumumab, Nimotuzumab, and Necitumumab, as listed in Table1. They work by impeding downstream signalling and the activation of immune elements such as natural killer (NK) cells 65. A significant mechanism of their action relies on antibody-dependent cellular cytotoxicity (ADCC). This is a type of immune reaction in which immune cells bind antibodies attached to cancer cells and release substances that eliminate them. Three more antibodies have been approved against ErbB2 for the treatment of breast and gastric cancers, and these are: Trastuzumab, Pertuzumab and Margetuximab. Trastuzumab binds to the extracellular domain IV of ErbB2 receptor, hindering its dimerization with other ErbB members 66. Pertuzumab targets the extracellular domain II to prevent ErbB2 receptor heterodimerization with other ErbB members, particularly ErbB3, and induces ADCC. Margetuximab functions by blocking ErbB2 receptor signalling through ADCC and possesses an engineered Fc (fragment crystallisable) region to enhance its ability to activate immune cells, leading to a better immune response compared to other anti-ErbB2 antibodies. The role of ErbB4 in driving cancer progression remains unclear and hence little research was conducted in investigating it further 67,68. Monoclonal antibodies are relatively large molecules and are unable to penetrate inside the cells, thus their targets are restricted to the exposed ectodomain of ErbB receptors and the development of therapy resistance.

Tyrosine kinase inhibitors (TKIs)

ErbB tyrosine kinase inhibitors offer significant benefits in being small molecules that can reach and be able to target the intracellular tyrosine kinase domain of the receptor. TKIs compete with ATP by binding to the ATP-binding pocket of the kinase domain, preventing the transfer of phosphate groups to tyrosine residues and halting the downstream signalling cascade 69. However, despite their initial clinical response, resistance rapidly develops to these TKIs 68. There are several generations of ErbB-TKIs, with generation 1 acting reversibly in binding to the ATP-pocket the receptor tyrosine kinase domain of the receptor and targeting ErbB1 and/or ErbB2. Examples of the first generation TKIs include Gefitinib (against ErbB1), Erlotinib (against ErbB1), Lapatinib (against both ErbB1 and ErbB2) and Tucatinib (against ErbB2), as shown in Table 1. Resistance quickly developed to the use of the first generation TKIs, particularly mediated by ErbB1 mutations in the form of T790M (threonine 790 to methionine), promoting studies to develop alternative molecules. Generation 2 of the ErbB-TKIs are irreversible inhibitors with longer and more potent action, characterised by their multiple ErbB receptor targets. Afatinib, Neratinib, and Dacomitinib are three of the approved drugs in this category. A pyrimidine-based generation 3 ErbB-TKIs were then developed to target more ErbB1 mutations, as well as the common T790M, without inhibiting the wild-type ErbB receptor 68. Examples of the approved third-generation ErbB-TKIs include

Osimertinib, Lazertinib, Mobocertinib, and Sunvozertinib. Generation 4 ErbB-TKIs is currently under development to counteract any resistance to previous therapies 61,68.

Miscellaneous approaches to targeting ErbB signalling in cancer

Despite the success of mAbs and TKIs in expanding cancer treatment, primary and acquired resistance have emerged, spurring studies into new avenues to improve the safe and effective targeting of ErbB receptors. One such area of interest involves the linking of ErbB mAbs to chemicals that can further enhance the antitumour effects (antibody-drug conjugates, ADCs). The linking of microtubulin inhibitors such as Emtansine to Trastuzumab has led to the approval of that combination in targeting ErbB2 for the treatment of breast cancer 70. Furthermore, the association of the topoisomerase 1 inhibitor, Deruxtecan, with Trastuzumab has also gained approval for targeting ErbB2 in the treatment of breast cancer (refer to Table 1) 71.

Using inhibitory peptides to target protein-protein interactions, such as those encountered between ligands and receptors or between two receptors during dimerization, is another interesting development. Several molecules are under clinical progression in this field 72,73.

Another promising advancement is the design of multi-specific (bi-, tri-, and tetra-specific) antibodies to enhance the efficacy of antibodies targeting ErbB receptors 74.

The small-scale size of nanobodies enables efficient tumour penetration and minimizes steric hindrance near targeted epitopes 75. Several nanobodies targeting ErbB1, ErbB2, and ErbB3 have been developed to target various regions of the receptor 76-78.

Targeting protein degradation has also recently emerged as an innovative approach. In one such strategy called PROTAC (proteolysis targeting chimera), the protein of interest is linked to an E3-ubiquitin ligase 79. In the ErbB-PROTAC system, there are three main components: a ligand that binds to ErbB, derives from one of its inhibitors (such as a TKI), a ligand that binds to an E3 ubiquitin ligase, and a linker that connects these two ligands. By bringing the E3 ligase near ErbB, the PROTAC triggers the cell's natural ubiquitin-proteasome system (UPS) to ubiquitinate the ErbB receptor and tag it for degradation. This choice can help overcome the acquired resistance mechanisms to ErbB signalling functions 80,81. Similarly, lysosome-targeting chimeras (LYTACs) have also recently emerged as viable candidates targeting ErbB receptors via the endosome-lysosome pathway. LYTACs are bispecific mAbs simultaneously targeting the extracellular domain of ErbB and a lysosome-targeting receptor 82.

Combining agents that target different pathways is an emerging strategy to prevent resistance. For example, the dual ErbB2 (HER2) blockade using trastuzumab and pertuzumab (targeting different HER2 epitopes) is a useful regimen in HER2-positive breast cancer 83. A combination of trastuzumab or cetuximab with a traditional chemotherapy agent is another approach to enhance the cell killing 84. The use of an ErbB inhibitor in combination with another agent targeting a parallel pathway or downstream signaling is also a worthwhile strategy. Furthermore, employing ErbB inhibitors in combination with immune checkpoint inhibitors such as pembrolizumab to stimulate an immune response against the tumour is another strategy 85.

Resistance to ErbB receptor signalling in cancer

Resistance to ErbB receptor signalling constitutes a major clinical challenge. The mechanisms through which such resistance develops are complex but can broadly be categorised into 1) alterations in the receptor itself, 2) selection of an alternative signalling, 3) cell phenotypic transformation, and 4) changes in the tumour microenvironment (TME) and pharmacokinetic issues.

Table 1: Approved therapies targeting ErbB receptors for the treatment of cancer

Therapy class	Drug	Target	Indication	EMA/FDA approval
Monoclonal antibodies (mAbs)	Trastuzumab	ErbB2	GC+BC	1998
	Cetuximab	ErbB1	CRC+HNSCC	2004
	Panitumumab	ErbB1	CRC	2006
	Nimotuzumab	ErbB1	Glioma+ HNSCC	2014
	Pertuzumab	ErbB2	BC	2012
	Necitumumab	ErbB1	NSCLC	2015
	Margetuximab	ErbB2	BC	2020
ADC	Trastuzumab-emtansine	ErbB2/ microtubule	BC	2013
	Trastuzumab-deruxtecan	ErbB2/ topoisomerase	BC	2022
TKIs 1st generation	Gefitinib	ErbB1	NSCLC	2003
	Erlotinib	ErbB1	NSCLC	2004
	Lapatinib	ErbB1/2	BC	2007
	Tucatinib	ErbB2	BC+CRC	2020
TKIs 2nd generation	Afatinib	Pan-ErbB	NSCLC	2013
	Neratinib	ErbB1/2/4	BC	2017
	Dacomitinib	ErbB1/2/4	NSCLC	2018
TKIs 3rd generation	Osimertinib	ErbB1/2/3	NSCLC	2015
	Lazertinib	ErbB1/2/3	NSCLC	2021
	Mobocertinib	ErbB1/2/3	NSCLC	2021
	Sunvozertinib	ErbB1/2/3	NSCLC	2023
Multikinase inhibitors	Vandetanib	ErbB1/VEGFR2/RET	TC	2011
	Brigatinib	ErbB1/IGF1R/ALK	NSCLC	2017

EMA=European Medicines Agency, FDA=US Food and Drug Administration, ADC=antibody-drug conjugate, TKIs=tyrosine kinase inhibitors, ErbB=refers to its origin in the erythroblastic b gene, VEGFR=vascular endothelial growth factor receptor, RET= a receptor kinase (rearranged during transfection), IGF1R=insulin-like growth factor 1 receptor, ALK=anaplastic lymphoma kinase. GC=gastric cancer, BC=breast cancer, CRC=colorectal cancer, HNSCC=head and neck squamous cell carcinoma, NSCLC=non-small cell lung cancer, and TC=thyroid cancer.

ErbB receptor alterations

This is a classic and very common mechanism often encountered in ErbB1-mutant lung cancer treated with the first generation TKIs such as erlotinib and gefitinib 86. In this situation, the T790M "gatekeeper" mutation emerges, raising the affinity of the kinase domain to ATP, making it harder for the drug to outcompete ATP for receptor binding. Mutations can also arise in the extracellular part of the ErbB receptor, as seen in HER2-positive breast cancer treated with trastuzumab. Such mutations can prevent Trastuzumab, being an antibody, from binding effectively to the receptor.

Selection of an alternative signalling pathway

A common bypass mechanism here is encountered in the treatment of ErbB1-mutant lung cancer when c-MET (also called hepatocyte growth factor receptor- HGFR) activates many of the same downstream signals as PI3K through ErbB3, thus making the ErbB1 blockade irrelevant 18. Also, ErbB2 amplification can act as a bypass track in cancers treated with ErbB1 inhibitors.

Cancer cells can have intrinsic or acquired mutations in key signalling nodes downstream of the receptor, making the receptor itself redundant. For example, activating mutations in PI3K or inactivating mutations in PTEN (being a tumour suppressor protein) can hyper-stimulate the PI3K/Akt pathway and its critical role as a survival signal 87. Also, activating mutations in BRAF or KRAS, which are common in colorectal cancers, can constitutively activate the MAPK pathway. This explains why KRAS-mutant colorectal cancers are intrinsically resistant to anti-ErbB1 antibodies like cetuximab 88.

Cell phenotypic transformations

Cancer cells can acquire a different phenotype following treatment, as documented in the change of an ErbB1-mutant non-small cell lung cancer after treatment with TKIs 89. The small-cell lung cancer is driven by different biology and is completely resistant to ErbB1-TKIs. Additionally, cancer cells can lose their epithelial traits and become more mesenchymal, known as epithelial-mesenchymal transition (EMT). The mesenchymal characteristics are associated with stem-like properties, invasiveness, and resistance to cancer therapies.

Changes in the tumour microenvironment and pharmacokinetics

Ineffective delivery or clearance of drugs targeting ErbB receptors can result in lower-than-therapeutic concentrations within the tumour. Such an incomplete inhibition may not effectively kill cancer cells but can select resistant subclones, making it harder to treat the cancer. The pharmacokinetic processes, including absorption, distribution, metabolism and excretion, are dynamic in nature creating transient fluctuations in drug levels. If these fluctuations lead to periods of sub-therapeutic drug concentration, even for a short period of time, they can promote the development of resistance 10,90. Tumour heterogeneity can add a further complicating dimension to the development of resistance. Not all cells with a tumour are identical, and a subpopulation could be intrinsically resistant, such as the case with KRAS-mutant cells 91. These mutant cells may be selected for and expanded with further cycles of division once the drug eliminates the sensitive cells.

Conclusion

The discovery of ErbB receptors and their signalling pathways provided a paradigm for understanding carcinogenesis and fundamentally shaped the landscape of precision medicine. The efficacy of targeting these receptors validated the principle that inhibiting the oncogenic drivers, embodied by ErbBs, can profoundly improve the clinical outcomes for patients. However, the almost inevitable emergence of resistance to therapies targeting the ErbB receptors highlights their dynamic and redundant nature. The key clinical challenge is overcoming the complex resistance mechanisms employed by cancer cells to avoid elimination. This often requires the use of combination therapies that aim to target the primary oncogenic driver and its most likely escape route, such as leveraging the power of antibody-drug conjugates. The continued research in this family of essential signal transducers will unveil new vulnerabilities and deliver new promising candidates in the fight against cancer.

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Conflict of Interest

The author declares no conflicts of interest related to this work.

Data availability

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Author Contributions

The author performed the literature review, revised the manuscript, and approved the final version.

The author meets the ICMJE criteria for authorship and agrees to be accountable for all aspects of the work.

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