The role of ErbB receptors in infection

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Key words

ErbB, EGFR, infection

Abstract:

Members of the epidermal growth factor receptor family (ErbB family) possess a wide distribution and diverse functions ranging from cellular growth to migration and apoptosis. Though highly implicated in a variety of cancers, their involvement in infectious disease is

less recognised. A growing body of evidence now highlights the importance of the ErbB family in a variety of infections. Their role as growth factor receptors, along with other characteristics, such as surface expression and continuous intracellular trafficking, make this receptor family ideally placed for exploitation by pathogens. Herein, we review our current understanding of the role of the ErbB family in the context of infectious disease, exploring the mechanisms that govern pathogen exploitation of this system.

ErbB receptors, a gatekeeper of infectious disease

The co-evolution of host and pathogen has ensured that while the host attempts to maintain immunological homeostasis, invading organisms look to manipulate host biology for their own benefit. A central role in this co-evolution is played by host cell receptors which can both recognise microbes and manipulate cellular responses to them. As such, pathogens have developed mechanisms to subvert host cell receptors for their own needs; the ErbB family is one group of host receptors involved in such a relationship.

The ErbB receptor tyrosine kinase family consists of four members, ErbB1 (epidermal growth factor receptor, EGFR), ErbB2, ErbB3 and ErbB4, which are expressed on a plethora of cell types, including epithelial [1], endothelial [2] , neuronal and glial [3], bone [4], adipose [5], liver [6] and cardiovascular cells [7]. Following ligand binding and activation, oligomerisation of ErbB family members occurs [8]. ErbB signalling is then induced through phosphorylation of intracellular domains, resulting in the activation of several major intracellular signalling pathways, including mitogen activated protein (MAP) kinase, nuclear factor kappa B (NF-κB), phosphoinositide 3 (Pi3) kinase and janus kinase/signal transducer and activator of transcription (JAK/STAT) pathways. ErbB associated signalling pathways govern a wide variety of outcomes including cell survival, proliferation, cell death/apoptosis, angiogenesis, adhesion, differentiation and migration/invasion.

The majority of studies investigating the role of ErbB receptors in infectious disease focus on pathogens that primarily infect mucosal surfaces. In this context, ErbB expression on epithelial cells, the primary point of pathogen contact, plays a crucial role. As membrane receptors, ErbB functionality and localisation make them well positioned to provide a direct

point of contact and entry into host cells. Not only are ErbB family members regularly endocytosed during their normal life cycle, but pathogen-ErbB ligation [9,10] and ErbB receptor signalling cascades [11–14] can contribute to cellular entry of a diverse range of microbes. Pathogen-mediated hijacking of ErbB signalling pathways also results in prolonged host cell survival [11,12,15–17] as well as altered immune responses [18–26], which may, in turn, enhance pathogen persistence. Crucially, however, their role as growth factor receptors may be required by intracellular organisms, dependent on host cell machinery for self-propagation, such as Hepatitis C virus (HCV) [15,27–29], Epstein Barr virus (EBV) [30] and Human papilloma viruses (HPV) [31]. These pathogens are able to regulate transition through host cell cycle checkpoints and indeed their association with ErbB receptors is linked to cellular transformation and oncogenesis. A direct correlation, however, between regulation of the cell cycle and oncogenesis, has not been shown.

ErbB receptors clearly exhibit a diverse and important range of functions. This review attempts to detail our current understanding of their role of during infection (summarised in Table 1) and contribution towards disease.

ErbB-dependent pathogen entry and invasion:

Influenza A virus (IAV), respiratory syncytial virus (RSV) and coronaviruses are respiratory pathogens that have been extensively studied in airway epithelial cells with regard to their replication cycle and the host response they elicit. More recently, it has been shown that all three viruses are able to utilise EGFR (ErbB1) for host cell entry. While RSV [32,33] and coronaviruses [34] induce EGFR-dependent macropinocytosis, a non-selective mechanism of internalising large bodies of extracellular material, IAV induces lipid-raft clustering on

surface membranes, resulting in EGFR activation and internalisation of both virus and EGFR [35]. Interestingly, lipid rafts are also important for IAV viral budding and exit from host cells [36–39]. Newly synthesised structural IAV proteins, hemagglutinin (HA) and neuraminidase (NA), can assemble at the cytoplasmic leaflet of lipid rafts [40,41], providing a platform for nascent viral proteins to cluster at, form progeny virus and from which to bud [42]. Given that EGFR localises at lipid rafts [43], a potential role for EGFR during viral exit may also exist (see Outstanding Questions Box). Additionally, the intestinal bacterial pathogen *Campylobacter jejuni* [44] also requires lipid-raft clustering and activation of raft-associated proteins, integrin-β1, EGFR and platelet derived growth factor receptor (PDGFR) for induction of filopodia formation and bacterial invasion.

While such pathogens exploit host internalisation mechanisms, some large microbes appear to have adopted a different mechanism of EGFR-mediated host cell entry, involving manipulation of epithelial junction proteins. The integrity of the epithelium is critical for host defence and is maintained by a variety of proteins located at the interface of adjacent epithelial cells, which include tight junctions, adherens, desmosomes and gap junctions. Such proteins help to maintain intimate contact between neighbouring cells, cellular anchorage and polarity, as well as the paracellular flux of solutes [45–48].

With this in mind, it becomes apparent that targeting such proteins may provide a means of breaching this primary defence barrier, and indeed EGFR has been implicated in modulation of such junction proteins. The bacterial species *Salmonella enterica serovar* Typhimurium is able to activate EGFR and induce expression of Claudin-2, a channel forming tight-junction protein [49] which results in gut epithelium invasion [50]. Claudin-2 activation during

infection is dependent on EGFR phosphorylation, as evidenced by a reduction in bacterial load following siRNA-mediated EGFR downregulation [50]. An alternative mechanism targeting junction proteins for cell entry is utilised by *Staphylococcus aureus*. Cleavage of occludin and E-cadherin, following EGFR activation, facilitates transmigration of *S. aureus* through cell-cell junctions, and inhibition of EGFR activity prevents *S. aureus* migration through an epithelial monolayer [13]. Additionally, *Neisseria gonorrhoeae* induces an EGFR-dependent mechanism of β-catenin redistribution from apical junctions to the cytoplasm, resulting in weakened apical junctions and gonococcal transmigration across the epithelium [51].

Unsurprisingly, enhanced epithelial cell proliferation and improved barrier integrity can provide protective functions against pathogen invasion [52–54], and interestingly both factors can be regulated by ErbB receptors. A protective role of ErbB receptors against infection would be interesting to explore in this context (see Outstanding Questions).

The second ErbB family member, ErbB2, is also targeted by pathogens for cellular entry. *Mycobacterium leprae* directly binds and activates ErbB2 to induce downstream Erk1/Erk2 signalling and bacterial invasion of Schwann cells. Trastuzumab, a potent ErbB2-targeted monoclonal antibody, abrogated both *in vitro* and *in vivo M. leprae*-induced myelin damage, highlighting ErbB2 as a crucial factor for leprosy disease [14]. The bacterium *Neisseria meningitidis* also induces recruitment and aggregation of ErbB2, but not other ErbB family members, on endothelial cell membranes, directly beneath sites of bacterial colony formation. Subsequent activation of ErbB2 and downstream Src-dependent signalling led to internalisation of *N. meningitides* and invasion of target cells [2]. Additionally, the fungus *Candida albicans* utilises both EGFR and ErbB2 to induce endocytosis and invasion into

epithelial cells [55,56]. Reduced severity of oropharangeal candidiasis is observed in mice following treatment with a dual EGFR/ErbB2 kinase inhibitor [55]. Liu et al. also document ErbB2 activation during vulvovaginal candidiasis in humans [57].

Another pathogen-mediated mechanism that promotes host cell entry may involve increased numbers of ErbB receptors at the cell surface. ErbB receptors spend the majority of their life span at the surface of cell membranes but continually undergo internalisation as part of normal processing. The fate of internalised receptors has important consequences for the cell. Potential receptor outcomes following endocytosis, include, recycling back to the surface (associated with proliferation), transport to other cellular compartments such as multivesicular bodies, the nucleus or mitochondria (related to homeostasis), or being targeted for degradation (thought to promote cell death) [58–60]. Pathogens appear to target these trafficking pathways for their own benefit. For example, Hepatitis C virus (HCV) induces the upregulation of host derived Netrin-1, which suppresses EGFR recycling, resulting in enhanced levels of surface EGFR, EGFR activation and subsequent viral endocytosis [27], which occurs via virus-induced EGFR and host-derived CD81 protein binding [28]. Additionally, the ErbB ligand neuregulin-1 has been implicated in enhancing EGFR and ErbB2 surface expression during HCV infection [29]. *N. gonorrhoeae*-induced upregulation of several ErbB ligands was also found to coincide with translocation of both EGFR and ErbB2 receptors to apical surfaces, following infection. This disruption of normal receptor distribution within polarised epithelial cells led to enhanced bacterial invasion and upregulation of EGFR-ligand mRNA was also observed [61]. Conversely, however, *Escherichia coli*-mediated disruption of endosome recycling leads to reduced surface EGFR, transferrin and β1-integrin expression [62]. Additional examples of EGFR-dependent

mechanisms of host cell entry include *Chlamydia pneumoniae* Pmp21-mediated recruitment of EGFR [10], and EGFR-dependent formation of HPV type 16 (HPV16), Annexin A2 and S100A10 heterotetramers to facilitate HPV16 infection [31]. Interestingly, malignant tissue from patients with HPV-associated cancers, often poorly express EGFR [63,64]. Further understanding of the connection between HPV and EGFR is required to fully appreciate this relationship.

ErbB-dependent host-directed internalisation and targeting of barrier integrity as well as ErbB trafficking, appear to be commonly used mechanisms of cellular entry by a diverse range of pathogens. The development of such distinct pathogen-specific mechanisms to achieve varied methods of internalisation, all of which utilise EGFR, clearly highlights the importance of these receptors as significant points of entry into host cells.

Prolonged host-cell survival through pathogen-mediated EGFR activation

ErbB-mediated host cellular entry is not the only function of this receptor family that is of potential benefit to invading organisms. ErbB receptors are potent mediators of cellular growth and survival, and unsurprisingly they have become a commonly exploited target for this purpose also. The association between Human cytomegalovirus (HCMV) and EGFR has been well studied. HCMV employs multiple mechanisms of modulating EGFR signalling for its own propagative benefit, including rapid induction of protein kinase B (PKB, alias Akt) activation, a protein kinase downstream of Pi3K with important roles in cell cycle regulation. Cojohari et al. showed that use of MK-2206, a highly selective Akt inhibitor during HCMV infection, results in decreased viability of infected monocytes [11]. While uninfected cells utilise the primary isoform of Pi3K (P110δ) for Akt signalling, a switch occurs in HCMV-

infected cells to allow use of the less dominant P110β isoform, resulting in prolonged cell survival past the 48 h cell-fate check point. While cell viability was dependent on P110δ activity in uninfected cells, inhibition of this predominant isoform did not cause apoptosis in HCMV-infected cells, which instead succumbed to cell death following P110β inhibition [11]. Furthermore, evidence of EGFR-associated promotion of anti-apoptotic proteins, myeloid leukemia sequence (Mcl-1) and heat shock protein 27 (HSP27) [12], as well as modulation of negative regulators of cell survival, such as phosphatase and tensin homolong (PTEN) and SH2 domain-containing inositol 5-phosphatase 1 (SHIP1) [11] has also been shown. In summary, HCMV appears able to activate EGFR signalling, utilise alternative signalling molecules in this pathway, and manipulate EGFR to selectively prevent cell apoptosis for its own propagative benefit.

Additional mechanisms to modulate the cell cycle via ErbB receptors include HCV-induced cell survival through amphiregulin release (AREG, an EGFR ligand) [15], *Helicobacter pylori* induced cell survival and hyperproliferation via EGFR activation [16] and also *Shigella flexineri* promotion of host cell survival through use of phosphatidylinositol 5-phosphate (PI5P), to impair lysosomal degradation and regulation of EGFR trafficking, as well as downstream signalling [17].

Mechanisms of increasing host infected cell survival appear to involve enhanced 'growth' stimulants while suppressing cell death mechanisms. The observation that HCMV, HCV, *H. pylori* and *S. flexineri* are all capable of invading and surviving within host cells suggests that their ability to prolong host cell survival is a specific and evolutionary targeted effect, induced for pathogen benefit.

Pathogen induced modulation of immune responses via EGFR:

The ability of pathogens to modulate host immune responses has been long established. However, the importance of ErbB receptors in this context is less known. A number of pathogens have been found to manipulate EGFR to promote immune evasion. IAV and Rhinovirus (RV)-16 are both capable of inhibiting interferon (IFN)-λ production, a critical antiviral cytokine of the airways, through an EGFR-dependent mechanism that results in enhanced viral titres [18]. Suppression of CXCL10 (IFN-γ induced protein 10 (IP-10)), a monocyte and T cell chemokine, has also been shown following IAV, RV or RSV infection, through virus-induced EGFR signalling [19]. Additionally, NF-kB, a primary transcription factor governing immune responses, is targeted during *Klebsiella pneumoniae* infection of bronchial epithelial cells [65]. Here, the EGFR/Pi3K/Erk signalling pathway is activated to result in diminished nuclear translocation of NF-kB [66], likely resulting in the suppressed activation of NF-kB and inflammatory responses observed during *K. pneumoniae* infection [65].

EGFR activation may also be involved in airway remodelling, which is a hallmark feature of chronic obstructive pulmonary disease (COPD) and asthma. Airway remodelling refers to the structural modifications of the airway tissue and can involve increased smooth muscle mass, sub-epithelial fibrosis and mucous gland hyperplasia which contribute to airflow obstruction and impairment of lung function. In a model of epithelial cell infection, stimulation with synthetic double stranded RNA (poly : IC) led to induction of EGFR- and downstream ERK/p38 MAPK- dependent mucin (MUC)-5AC, transforming growth factor (TGF)-β1, matrix metalloproteinase (MMP)-9 and vascular endothelial growth factor (VEGF) cytokine

expression, all of which contribute to airway remodelling [21]. *Pseudomonas aeruginosa* [25] and poly(I:C)-mediated [26] activation of EGFR, also enhanced MUC5AC and subsequent mucus hypersecretion, which contributed to airway mucus obstruction during respiratory disease [25,26].

Retention of MHC-I molecules at the Golgi, by the bacterium *Brucella abortus* is another example of immune evasion via ErbB receptors and results in inhibited MHC-I surface expression [22,67]. Inhibition of EGFR, ErbB2 or the ErbB ligand sheddase protein, tumour necrosis factor-α-converting enzyme (TACE/ADAM17), was each able to modestly recover MHC-I surface expression, whilst Erk1/2 inhibition led to significant restoration of MHC-I surface expression [22]. Furthermore, exposure of the monocyte/macrophage cell-line THP-1, to exogenous EGF, TGF-α or a combination of the two EGFR ligands, was able to mimic *B. abortus*-induced retention of MHC-I at the Golgi and reduced surface MHC-I expression.

Interestingly, Hepatitis B virus (HBV) can promote immune evasion by inducing tolerance. Surface EGFR is upregulated on HBV infected intrahepatic regulatory T cells (Treg), which enhances their immunosuppressive capacity [68]. HBV-infected mice exhibited increased numbers of Treg cells that expressed immunosuppressive cytokines such as interleukin (IL)-10 and TGF-β, in addition to an enhanced ability to prevent CD8+ T cell proliferation, a requirement for HBV clearance [68]. HCMV induced latency is another interesting tactic providing immune evasion and also governed by EGFR activity. During infection, ability to induce latency-associated *UL138,* while suppressing *IE1/IE2* lytic genes, was shown to be EGFR dependent, by use of EGFR specific inhibitors [69]. Additionally, *Mycobacterium tuberculosis* can utilise EGFR-induced p38/MAPK signalling pathways within macrophages,

to prevent proper anti-microbial macrophage responses, resulting in enhanced murine infection [70]. However, in contrast to these pathogen-driven functions of EGFR that contribute to infection, some EGFR-induced host protective functions have also been observed. One study highlights the requirement of EGFR in macrophage activation and function against *H. pylori* bacteria, where EGFR-deficient macrophages exhibited impaired T helper (Th)1 and Th17 adaptive responses, resulting in suppressed *H. pylori*-induced chronic inflammation and disease progression in mice [71]. Additionally, EGFR-dependent *S. aureus*-induced IL-1α and IL-1β [23], as well as *E. coli*- [24] and virus induced [72–74] IL- 8, may be examples of host-beneficial EGFR-dependent responses induced by pathogens.

Together, these studies highlight a complexity of EGFR functionality, which has ability to both contribute to and protect against infections. Mechanisms for immune modulation are highly diverse and pathogen-specific, perhaps emphasising the strength of our intricate immune system and the specialisms of each microbial species. The observation that pathogens are able to augment cellular immune responses through EGFR signalling, again highlights the importance of this class of receptors during infection.

ErbB associated cancers

ErbB receptor activity is highly associated with oncogenic transformation. Several cancers, including head and neck squamous cell carcinoma (HNSCC), lung and colon cancers, are known to result from aberrant ErbB expression or signalling. Aberrations leading to overexpressed or constitutively active ErbB receptors [75–77], overproduced ErbB receptor ligands [15,78–83] and sheddases that cleave ErbB precursor ligands into their mature forms [84–87], have all been shown to cause cellular transformation. Thus, it is perhaps

unsurprising that several cancer-inducing pathogens have been found to promote ErbB activation, with evidence of cellular transformation being directly caused by pathogen induced ErbB signalling. In fact, the ErbB signalling pathway has been implicated in a number of major oncogenic virus infections.

For example, HBV has been shown to induce upregulated expression of EGFR gene and protein, both of which are strongly associated with hepatocellular transformation [88,89]. This virus is also thought to enhance ErbB2 mRNA stability through the HBV-encoded X-protein (HBx), which is itself strongly associated with hepatocellular carcinoma (HCC), resulting in enhanced HCC cell migration [90]. Likewise, HCV infection results in enhanced surface EGFR expression [29,61], EGFR activation and consequent viral entry [28], whilst patients exhibiting certain EGFR polymorphisms spontaneously clear HCV infection [91]. HCV induced AREG overexpression in human hepatoma cells, contributes to prolonged infected-cell survival, cirrhosis and HCC progression [15]. Furthermore, EGFR, which can also be cleaved from apoptotic cells to shut down signalling [92], is found in significantly higher concentrations in HCC patient plasma, in the presence of HCV and HBV infection [93]. Whether this reflects host attempts to curtail aberrant cell proliferation, or is merely a by-product of virus induced apoptosis, remains unclear. So consistent is the increase in soluble EGFR during virus-induced HCC, that it may serve as a marker for such disease [93].

HPV is another virus which has been associated with both EGFR and oncogenesis. Interestingly, in this case, EGFR expression is commonly low [63,64] and has been an area of detailed investigation. One explanation for the existence of ‘HPV-positive EGFR-negative’ malignancies could lie in the functional redundancy between ErbB receptors as well as an

ability of family members to regulate expression of each other. Indeed, several studies have highlighted an over-expression of ErbB2 and ErbB3 receptors, or even ErbB3 dependency [94], in HPV-positive cancers [95–97], whilst Stindt et al. showed that HCV induced downregulation of ErbB3, upregulates EGFR and ErbB2 expression on hepatocytes [29]. These results were reproducible following suppression of ErbB3 with siRNAs and suggests that ErbB3 can function to impact on the expression of EGFR and ErbB2 [29]. However, the presence of 'HPV-positive EGFR-positive' malignancies has also been observed [98,99]. Together, these examples highlight an association between HPV-induced cancer and ErbB receptors, though the full extent of receptor contribution to such disease remains incompletely understood.

Other oncogenic viruses found to have association with EGFR include Epstein Barr Virus (EBV), whose virus-encoded LMP1 protein induces EGFR expression [30], Kaposi's Sarcoma-associated Herpesvirus (KSHV), which promotes EGFR activation [100] and human T cell leukaemia virus (HTLV), shown to directly induce EGFR-dependent cellular transformation [101].

Additionally, bacteria-induced EGFR-dependent oncogenesis has been documented. The association between *H. pylori* and gastric cancer is highly acknowledged, with studies suggesting that this pathogen remains the strongest known risk factor for stomach tumorigenesis. Early clearance of infection significantly lowers the risk of malignancies [102], which supports its role as a carcinogen and crucially, *H. pylori* infections are strongly linked to the dysregulation of EGFR ligands and/or transactivation of EGFR (reviewed in [103]). The ability of *H. pylori* to dephosphorylate EGFR, is particularly interesting. Pathogen

induced inactivation of EGFR involves activation of host SHP2 tyrosine phosphatase, to result in suppression of the antimicrobial peptide, human beta-defensin 3 (hBD3) expression, to which *H. pylori* is highly susceptible, and sustained bacterial infection [104].

It is curious to note that the ErbB-dependent oncogenic pathogens mentioned herein are capable of replicating intracellularly. Coupled with their ability to induce hyperproliferation, it would be interesting to investigate the role of host cell turnover in ErbB-dependent pathogen survival. Several viruses (HBV, HCV, EBV and HPV among others) are known to require host machinery for protein synthesis and subsequent viral replication; these host translational apparatus can be found in greater abundance at specific points during host cell cycle [105]. As such, subversion of the cell cycle is a common theme where both cycle arrest and induction may occur [106], however the effect of either on associated disease remains unclear. Indeed, not all viruses possessing the ability to regulate the cell cycle, such as IAV and SARS viruses, are particularly associated with oncogenesis. Further investigation into the precise requirements of oncogenic pathogens, leading to host cell survival and replication, and the role of ErbB receptors in this context, may provide valuable insights to developing more effective cancer therapies.

Concluding remarks and future perspectives

There exists a growing body of evidence to support the role of the ErbB receptor family as a critical regulator of pathogen invasion and propagation within the human host. Numerous studies have highlighted pathogen-selective exploitation of ErbB receptors as a mechanism that contributes to host cell entry, cell survival, augmentation of host immunity and cancer (Fig 1, Key Figure). Their cellular localisation, regulated mode of internalised recycling and

functional capacity, make the ErbB family an excellent target for pathogens that require access into host cells in order to self-replicate. Several ErbB-dependent pathogens show capacity to regulate the cell cycle to access host machinery, however the direct effects of this on prolonging host cell survival or enhancing proliferation remain undefined. Malignancies do not occur as a result of all infections and suggests there are likely other factors involved in driving cellular transformation during infection.

On a grander scale, the role of host ErbB receptors during infection is an overlooked aspect of disease which warrants deeper consideration. To date, research in this context has focused predominantly on viral pathogens, with much less detail known regarding bacterial and fungal infections. Investigations are also skewed toward the more prominent EGFR and interest in this host receptor may be warranted as it is the only ErbB member to undergo ligand-induced internalisation, greatly enhancing its appeal for pathogen exploitation. However, given the functional redundancy of ErbB receptors and their potential to regulate expression of each other [29], it would be remiss not to fully investigate the role of all family members. With drug resistance increasing in a plethora of pathogens, there is an immediate and critical need for the development of innovative therapies that target novel factors. As such, ErbB receptors and associated signalling pathways may possess potential value as novel therapeutic targets during pathogenic infection. This notion is supported by a recent study which validates the efficacy of the specific EGFR inhibitor Erlotinib, in conjunction with a broad spectrum tyrosine kinase inhibitor Sunitinib, against a range of evolutionary distinct viral pathogens [107]. Both drugs have FDA approval as immunomodulatory cancer therapies and would also be exciting prospects as novel anti-microbial drugs. However, toxicity concerns that include adverse skin conditions, diarrhoea

364 and heart failure may warrant limitation of their use to treatment of more serious
365 infections.
366
367 The future of both research and therapies surrounding ErbB receptors is continually
368 expanding and the next decade should reveal some intriguing and critical information
369 regarding the interaction between microbes and these receptors.

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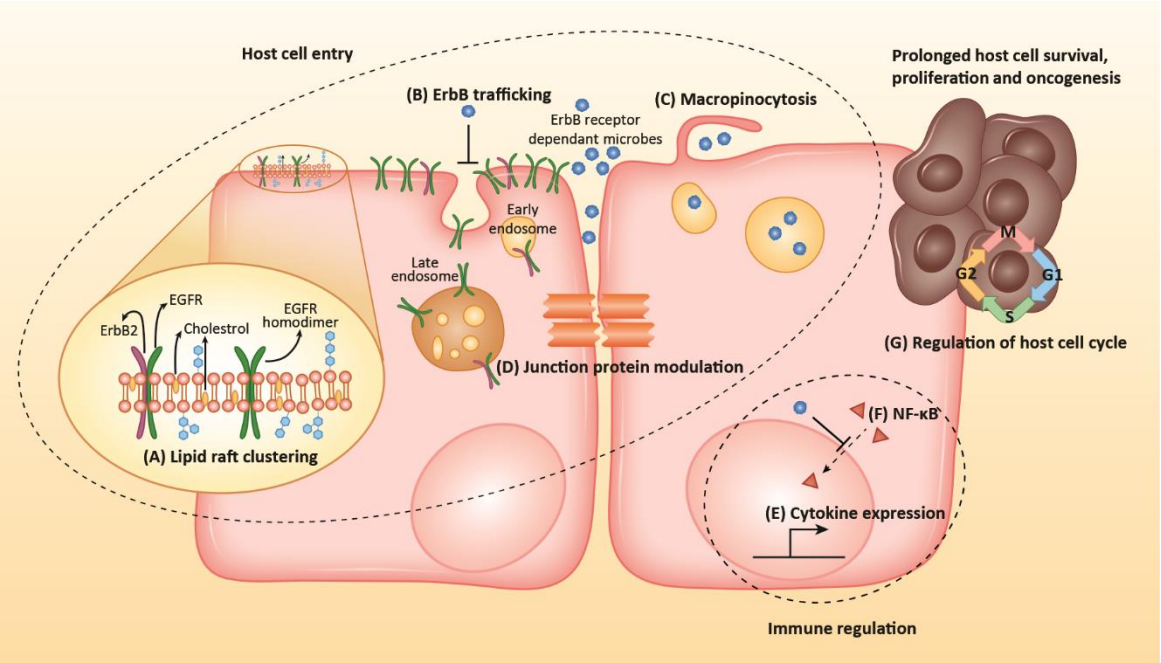
Key Fig: Primary mechanisms and targets modulated or induced by microbes, involving ErbB receptors.

Pathogen induced mechanisms of host cell entry can involve (A): ErbB-mediated lipid raft clustering, (B): inhibition of ErbB endocytosis resulting in elevated surface receptor expression, (C): ErbB-mediated macropinocytosis and (D): modulation of junction proteins. Pathogens can also manipulate factors that govern immune responses through ErbB receptor exploitation. Mechanisms here include (E): altering cytokine expression in infected cells and (F): inhibition of NF-κB nuclear-translocation. Additionally some pathogens that are able to regulate the cell cycle also appear able to induce host cell survival, proliferation or oncogenesis (G).


Host cell entry
(B) ErbB trafficking
ErbB receptor dependant microbes
(C) Macropinocytosis
Prolonged host cell survival, proliferation and oncogenesis
Early endosome
Late endosome
EGFR
ErbB2
Cholestrol
EGFR homodimer
(A) Lipid raft clustering
(D) Junction protein modulation
M
G2
G1
S
(G) Regulation of host cell cycle
(F) NF-κB
(E) Cytokine expression
Immune regulation

Outstanding questions box:

- The EGFR has been associated with lipid raft clustering and viral entry mechanisms, but lipid raft aggregation is also involved in viral egress. Does EGFR, therefore, play a role during budding of nascent viral progeny?

- Both enhanced cell turnover and barrier integrity have been shown to be protective against pathogen invasion, factors that ErbB receptors are directly capable of inducing. Is there potential to enhance this protective role of ErbB receptors as a preventative measure against infection?

- How efficacious would current ErbB targeted therapies be against pathogen infection in humans? Toxicity and resistance against such drugs has been observed in cancer patients. Are the mechanisms behind such events relevant in the setting of pathogenic infection?

- Is ErbB receptor function capable of directly driving pathogen-induced cellular transformation? If so, at which stage(s) of cancer does this contribute? During initial oncogenesis or maintenance and progression of cancer?

Table 1: ErbB-dependent microbes and their mechanisms of receptor exploitation

Virus	Mechanism of ErbB exploitation	Outcomes	Ref.
EBV	Induces of EGFR expression	Host cell proliferation	[30]
HBV	Induces of surface EGFR expression	Host cell proliferation	[88,89]
HCV	Disrupts EGFR recycling to enhance surface expression through host protein Netrin-1	Host cell entry	[27]
	Enhances EGFR and ErbB2 surface expression through NRG-1 dependant mechanism		[29]
	Induces AREG-dependant circumvention of apoptosis; induces proliferation and transformation	Host cell survival and proliferation	[15]
HCMV	Alters EGFR signalling molecules to bypass cell-fate check points and enhance production of cell cycle proteins	Host cell survival	[11,12]
	EGFR activation promotes latency by inducing latent, but suppressing of lytic gene expression	Immune evasion	[69]
HPV	Induces EGFR-dependent translocation of AnxA2 results in formation of the HPV-AnxA2-S100A10 binding complex required for viral entry	Host cell entry	[31]
HTLV	Induces EGFR activation resulting in cellular transformation in $CD4^+$ Tcells	Host cell proliferation	[101]
IAV	Induces of lipid raft clustering. Activates EGFR and other RTKs leading to cellular internalisation	Host cell entry	[35]
	Suppresses IFN-λ and CXCL10 through EGFR activation	Immune modulation	[18,19]
KSHV	Oncogenic pathogen induces activation of EGFR signalling	Unconfirmed	[100]
RV	Suppresses RV-induced IFN-λ and CXCL10 expression via EGFR activation	Immune modulation	[18,19]
RSV	Induces EGFR dependent macropinocytosis	Host cell entry	[32,33]
	Suppresses RSV-induced CXCL10 expression via EGFR activation	Immune modulation	[19]
SARS	Induces EGFR dependent macropinocytosis	Host cell entry	[34]

Table 1 continued:

Bacteria	Mechanism	Outcomes	Ref.
Brucella abortus	Inhibits MHC-I expression potentially involving EGFR, ErbB2 and/or TACE sheddase.	Immune modulation	[22,67]
Campylobacter jejuni	Induces lipid raft clustering and EGFR activation	Host cell entry	[44]
Chlamydia pneumoniae	Bacterial Pmp21 adhesin directly binds EGFR	Host cell entry	[10]
Escherichia coli	Disrupts endosome trafficking resulting in diminished surface EGFR	Unconfirmed	[62]
Helicobacter pylori	Induces EGFR dependent β-catenin nuclear translocation and PI3K/Akt signalling	Host cell survival	[16]
	Dephosphorylates EGFR to inhibit hBD3 expression and promote infection	Immune modulation	[104]
Klebseilla pneumoniae	Induces EGFR dependent inhibition of NF-kB translocation	Immune modulation	[65,66]
Neisseria gonorrhoeae	Induces redistribution of β-catenin from apical junction to cytoplasm through EGFR activation.	Host cell entry	[51]
	Induces translocation of ErbB2 and ErbB3 to apical surfaces		[61]
Neisseria meningitidis	Recruits and activates ErbB2 receptors	Host cell entry	[2]
Mycobacterium leprae	Directly binds ErbB2 receptors	Host cell entry	[14]
Mycobacterium tuberculosis	Prevent proper macrophage function resulting in enhanced infection	Immune modulation	[70]
Salmonella Typhimurium	Induces Claudin 2 expression through EGFR and downstream JNK activation	Host cell entry	[50]
Shigella flexineri	Induces PI5P production to regulate EGFR trafficking	Host cell survival	[17]
Staphylococcus aureus	Cleaves junction proteins occludin and E-cadherin to facilitate transmigration. EGFR activation is required	Host cell entry	[13]
Fungi	**Mechanism**	**Outcomes**	**Ref.**
Candida albicans	EGFR and ErbB2 dependent endocytosis	Host cell entry	[55,56]

Trends box:

- A wide and diverse variety of microbes have each evolved distinct mechanisms to exploit ErbB receptors, highlighting this receptor kinase family as a critical factor in initiation and maintenance of pathogen infections.
- ErbB family members are utilised by pathogens attempting to gain cellular entry, subvert immune responses, and manipulate the cell cycle of infected host cells. These events support and are necessary for pathogen persistence.
- Pathogen-mediated ErbB-exploitation may contribute to cellular transformation and oncogenesis in a variety of cancers.
- The use of existing FDA approved drugs that target ErbB receptors and associated signalling components may offer potential future therapies against infection.