Trends in Microbiology

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Review

The Role of ErbB Receptors in Infection

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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 coevolution 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 coevolution 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,

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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.

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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 nonselective 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). 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