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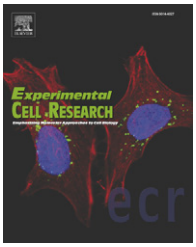

Review

ErbB receptors in the biology and pathology of the aerodigestive tract

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ABSTRACT

The most common sites of malignancies in the aerodigestive tract include the lung, head and neck and the esophagus. Esophageal adenocarcinomas (EA), esophageal squamous cell carcinomas (ESCC), and squamous cell carcinomas of the head and neck (SCCHN) are the primary focus of this review. Traditional treatment for aerodigestive tract cancers includes primary chemoradiotherapy (CRT) or surgical resection followed by radiation (or CRT). Recent developments in treatment have focused increasingly on molecular targeting strategies including cetuximab (a monoclonal antibody against epidermal growth factor receptor (EGFR)). Cetuximab was FDA approved in 2006 for treatment of SCCHN, underscoring the importance of understanding the biology of these malignancies. EGFR is a member of the ErbB family of growth factor receptor tyrosine kinases. The major pathways activated by ErbB receptors include Ras/Raf/MAPK; PI3K/AKT; PLCγ and STATs, all of which lead to the transcription of target genes that may contribute to aerodigestive tumor progression. This review explores the expression of ErbB receptors in EA, ESCC and SCCHN and the signaling pathways of EGFR in SCCHN.

Contents

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Introduction

The aerodigestive tract encompasses the lungs, esophagus, oral cavity, nasal cavity, paranasal sinuses, pharynx and larynx. The three most common sites where malignancies arise include the lung, head and neck and esophagus. This review will focus on esophageal adenocarcinomas/squamous cell carcinomas and squamous cell carcinoma of the head and neck (SCCHN). The primary risk factors in SCCHN include tobacco and alcohol use [1,2]. A subset of SCCHN has been shown to be caused by the human papillomavirus, primarily types 16 and 18 [2,3]. There is a high incidence of synchronous and metachronous esophageal squamous cell carcinoma (ESCC) in patients diagnosed with SCCHN, indicating the common biology of these aerodigestive tract neoplasms [4–7]. A recent report noted that ESCC accounts for approximately 38% of esophageal cancers in the United States (1998–2003) [8]. Established risk factors for ESCC also include tobacco and alcohol use [9] with esophagitis/inflammation as a possible contributing variable [10].

Esophageal adenocarcinoma (EA) is responsible for ~56% of esophageal cancers in the United States (1998–2003) [8] and has several established risk factors including Barrett's esophagus [11,12], gastro-esophageal reflux [13,14] and obesity (independent of reflux) [15–17]. Medications that relax the lower esophageal sphincter may also contribute but the current evidence is inconclusive [18]. Some reports suggest that *Helicobacter pylori* and the regular use of non-steroidal anti-inflammatory drugs may contribute to a reduced risk of EA [18].

Treatment for aerodigestive tract cancers including SCCHN and ESCC/EA has traditionally included primary chemoradiotherapy (CRT) or surgical resection followed by radiation (or CRT). Cetuximab is a monoclonal antibody against EGFR that has been shown to reduce patient mortality and increase locoregional control of the tumor when combined with radiotherapy in SCCHN [19]. In 2006 cetuximab became the first molecular targeting strategy approved by the FDA for SCCHN. Preliminary work in ESCC has shown that cetuximab can induce antibody-dependent cell cytotoxicity in ESCC cell lines [20]. A recent phase II clinical trial reported that cetuximab can be safely administered in combination with chemotherapy and radiotherapy in esophageal carcinomas without increased mucosal toxicity [21]. A phase III clinical trial is currently underway to determine if cetuximab in combination with CRT treatment will increase survival compared to CRT alone [21]. The success of this molecular targeting strategy in SCCHN and esophageal carcinomas underscores the importance of understanding the biology of these malignancies.

Biology of ErbB receptors in the aerodigestive tract

ErbB receptors are members of the ErbB growth factor receptor tyrosine kinase family and are generally found on the cell surface. ErbB receptors contain an extracellular ligand binding domain, a transmembrane region and an intracellular domain with tyrosine kinase activity (except ErbB3). Upon ligand binding, the receptors dimerize and autophosphorylate thereby initiating a signaling cascade downstream of the dimer. Ligand binding induces a conformation change of the receptor ectodomain (creating an extended and stabilized conformation, except for ErbB2 which constitutively maintains the stabilized conformation and has no known ligand [22]) to facilitate receptor dimerization [23]. ErbB ligands are produced as transmembrane precursors and the ectodomains are processed via proteolysis leading to the shedding of soluble growth factors [24]. In normal tissues this signaling cascade is tightly controlled and regulates processes that include epithelial development and injury response. The major pathways activated by ErbB receptors include Ras/Raf/MAPK; PI3K/AKT; PLCγ and STATs, all of which lead to the transcription of target genes that may contribute to aerodigestive tumor progression [25]. Regulation of ErbB receptor signaling occurs through temporal and spatial expression of receptor ligands and through receptor endocytosis. Endocytic trafficking leads to receptor recycling or ubiquitination and lysosomal degradation of the receptor [26].

EGFR activation can be induced through autocrine or paracrine ligands. There are six major EGFR ligands that are expressed at the mRNA level in some, but not all, SCCHN cell lines including: heparin binding EGF (HB-EGF), transforming growth factor alpha (TGF-α), betacellulin, amphiregulin (AR), heregulin, and epidermal growth factor (EGF) [27]. TGF-α and AR are the primary ligands implicated in autocrine growth signaling [28]. EGFR can homodimerize or heterodimerize with other members of the ErbB receptor family [29].

ErbB2 has no known exogenous ligands that directly bind to it. If ErbB2 is highly overexpressed it can spontaneously dimerize and autoactivate, but it is most commonly activated *via* heterodimerization with other ErbB family members [22]. ErbB3 has no intrinsic tyrosine kinase activity but is transactivated by EGFR and ErbB2. ErbB3 ligands include neuregulins, heregulin and neu differentiation factor [30]. ErbB4 can homodimerize or heterodimerize with other members of the ErbB receptor family. ErbB4 ligands include neuregulins, epiregulin, heregulin, neu differentiation factor, and betacellulin [30].

ErbB receptors in aerodigestive tract development

Knockout of each of the ErbB family members in mouse models leads to early stage lethality, limiting the study of ErbBs in the development of the aerodigestive tract. ErbB1 null mice had a generalized epithelial immaturity and multiorgan failure [31]; these mice have a short postnatal survival period in which impaired epithelial development in various organs is observed,