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Integrating genomics in head and neck cancer treatment: Promises and pitfalls

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Contents

Abstract

Head and neck squamous cell carcinomas (HNSCC) represent a multifactorial disease of poor prognosis. They have lagged behind other cancers in terms of personalized therapy. With expansion and high throughput sequencing methods, recent landmark exonic studies and

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Cancer Genome Atlas data have identified genes relevant to carcinogenesis and cancer progression. Mutational profiles and rates vary widely depending on exposure to carcinogens, anatomic subsites and human papilloma virus (HPV) infection. Tumors may exhibit specific, tissue-specific, not exclusively HPV-related, gene alterations, such those observed in oral cavity cancers in Asia or Occident. Except for the PI3K pathway, the rate of mutations in HPV+ cancers is much lower than in tobacco/alcohol-related cancers. Somatic driver mutation analyses show that relatively few driver genes are druggable in HNSCC and that tumor suppressor gene alterations prevail. More mature for therapeutic applications is the oncogenic PI3K pathway, with preclinical human xenograft models suggesting that *PI3KCA* pathway mutations may be used as predictive biomarkers and clinical data showing efficacy of mTOR/Akt inhibitors. Therapeutic guidance, to date, relies on classical histoprognostic factors, anatomic subsite and HPV status, with integration of hierarchized supervised mutational profiling to provide additional therapeutic options in advanced HNSCC in a near future. Unsupervised controlled genomic analyses remain necessary to unravel potentially relevant genes.

Keywords: Head and neck cancer; Human papilloma virus; Mutation; Gene; Sequencing; Druggability

1. Introduction

Head and neck cancer, of which 90% are squamous cell carcinomas (HNSCC), represents 600,000 new cancers worldwide each year. Two thirds present at an advanced stage and despite treatment advances, the five-year survival rate does not exceed 50%. HNSCC are multifactorial and heterogeneous in terms of tumor sites, histologies and exposure to carcinogens. No prognostic biomarker has yet provided a means to predict the response to treatments counteracting oncogenic processes. In contrast, other tumor types have shown targetable signaling pathways and specific genomic alterations relevant to treatment outcomes [1]. Screening for HER 2 amplification in breast cancers, BRAF mutations in melanomas, epidermal growth factor receptor (EGFR) tyrosine kinase mutations or ALK expression in non-small cell lung carcinoma and JAK2 in hematologic malignancies has become routine practice. Recently, mutations in PIK3CA in 30% of breast cancers, FGFR2 in 20% of endometrial and lung cancers have been investigated in clinical trials. By identifying relevant actionable genes in specific tumor types, next generation sequencing (NGS) has opened a new era of personalized therapy in many cancers. This review aims to shed light on clinically relevant and druggable somatic mutations involved in HNSCC.

2. Material and methods

A systematic search of the literature in PubMed was performed (before 9/2014) with the terms: HNSCC (restricted to mucosal carcinomas, excluding salivary gland, sinonasal cancers and mucosal melanomas) AND human papilloma virus (HPV) (68 references), mutation (68), oncogene (7700), tumor suppressor gene (TSG) (5170), driver (51), genomics (633), genetics AND sequencing (1592). Polymorphisms that might confer a genetic susceptibility to HNSCC [2] or epigenetic variations and chromosomal/copy number alterations were not specifically addressed. We further analyzed the Cancer Genome Atlas (TCGA) data and recent TCGA publication [3].

2.1. EGFR is paradoxically not actionable

Following the discovery that EGFR overexpression was deleterious, research has failed to show consistent prediction of response to EGFR inhibitors by EGFR overexpression or *EGFR* amplification [4]. Of note, EGFRvIII, a truncated EGFR variant, of presumed relevance in HNSCC [56], has been found associated with PI3K pathway activation [5,6]. However, recent data add to the controversy and rather suggest that EGFRvIII is not relevant in HNSCC [7]. Although most lung and head and neck carcinomas share exposure to tobacco, their activating mutations differ, underlining the tissue-specific nature of malignancies despite exposure to similar carcinogens [8]. Consistent genomic alterations have been lacking and relevant molecular means have failed to guide anti-EGFR therapeutics [9] in HNSCC to date. However, some downstream network elements might be clinically relevant and druggable.

Several pathways could be responsible for the resistance to EGFR monoclonal antibody treatment. As EGFR is part of the ErbB family receptors and as such, can be a heterodimerization partner for other ErbB. receptors. Dimerization with HER2 can lead to an asymmetric phosphorylation which could in turn activate one or the other pathways [10]. While specific data for head and neck cell lines are scarce, the resistance to HER2 in breast cancer cell lines has been proven to be linked to EGFR/HER2 dimers [11]. Oppositely, when HNSCC cell lines are exposed to gefitinib, elevated levels of ErbB2 and ErbB3 protein expression are associated with gefitinib resistance [12]. Addition of HER2 inhibitors or pan-HER inhibitors has been suggested as a solution to overcome this mechanism [12,13]. Interaction between MET and HER3 could shunt the EGFR pathway and activate the downstream AKT signaling pathway with HER3 phosphorylation by MET bypassing ErbB2/ErbB3 heterodimerization [14]; inhibition of both pathways is warranted to be effective. Src signaling pathway can be activated by EGFR but can also activate MET independently of EGFR which could also explain anti-EGFR therapy resistance [15].