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Understanding c-MET signalling in squamous cell carcinoma of the head & neck

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ABSTRACT

c-MET is a membrane spanning receptor tyrosine kinase for hepatocyte growth factor (HGF) also termed scatter factor. Transmitting signals from mesenchymal to epithelial cells, the HGF/c-MET axis mediates a range of biological processes that stimulate proliferation, motility, invasiveness, morphogenesis, apoptosis, and angiogenesis. Aberrant c-MET signal transduction favours tumorigenesis with the acquisition of invasive and metastatic phenotypes. Biological functions of c-MET may strongly vary according to microenvironmental changes, which occur at different stages of tumorigenesis and include also HGF/c-MET activation in stromal cells. In this review, we focused on abnormalities in non-nasopharyngeal squamous cell carcinoma of the head & neck. While the prevalence of c-MET mutations and amplifications ranges 0–25%, c-MET upregulation can be found in the majority of squamous head & neck carcinomas. Despite marked heterogeneity in published scoring methods, immunohistochemical overexpression of c-MET has been typically linked to advanced stages and associated with impaired survival and/or resistance to radiotherapy, chemoradiotherapy, and cetuximab. Experimental studies in cell lines and patient-derived xenografts using various c-MET antagonists (both as single-agents and in combination with cytotoxic and epidermal growth factor receptor [EGFR]-directed agents) yielded promising results, albeit benefit in clinical trials remains to be demonstrated. Consequently, selecting more active agents and integrating them effectively in studies, which incorporate predictive biomarkers such as c-MET gene mutations, amplifications, and overexpression, remains challenging. Further investigations should increase emphasis on disentangling the role of tumour-stromal interactions and analyse their potential as modifiers of drug response.

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1. Introduction

Squamous cell carcinoma of the head & neck (SCCHN) comprises more than 90% of malignancies arising from the mucosal lining of the upper aerodigestive tract (Barnes et al., 2005). According to the GLOBOCAN worldwide estimates for 2012, cancers of the lip, oral cavity, pharynx, and larynx accounted together for 686,300 new cases and 375,700 cancer deaths, thus ranking seventh in both the incidence and mortality and fifth in the 5-year prevalence among all reported cancers (excluding non-melanoma skin tumours) (Torre et al., 2015). In the case of early stage disease, single-modality treatments with either surgery or radiotherapy achieve cure rates around 80%. Unfortunately, the majority of patients still present with advanced tumours where despite multimodality approaches, the prognosis remains dismal. In locoregional SCCHN, five-year overall survival does not exceed 60% with the notable exception of human papillomavirus (HPV)-driven oropharyngeal cancer, where the rate reaches over 80% (Howlader et al., 2016; O'Sullivan et al., 2016). When recurrence or distant metastases develop, the disease is usually resistant to radiation therapy and chemotherapy, and only palliative strategies are generally applicable with an expected survival outcome of 6–10 months (Szturz and Vermorken, 2016).

Recently, new insights into the complex molecular network involved in SCCHN pathogenesis have opened a promising era of translational research aiming to identify novel anticancer therapies guided by reliable biomarkers. Mesenchymal-epithelial transition factor (c-MET) is a membrane spanning receptor tyrosine kinase for hepatocyte growth factor (HGF, also known as scatter factor) (Bottaro et al., 1991). HGF/c-MET-related aberrant signal transduction is biologically associated with changes in cellular processes that can trigger acquisition of invasive and metastatic phenotypes. This review article summarizes the current knowledge about the role of the c-MET receptor in squamous cell carcinoma of the oral cavity, larynx, oro- and hypopharynx, bringing up possible avenues for further investigations and attempting to answer the fundamental question whether c-MET represents an actionable target in precision medicine of SCCHN.

2. Historical background of the c-MET discovery

For the past three decades, systematic efforts have been made towards refining the knowledge about c-MET signalling in the pathophysiology of human cancer. First reports of HGF, structurally related to plasminogen, date back to the early 1980s when two research groups isolated and further characterized a new substance responsible for liver regeneration in the serum of partially hepatectomized rats (Michalopoulos et al., 1982; Nakamura et al., 1984; Michalopoulos et al., 1984; Thaler and Michalopoulos, 1985). Also referred to as hepatotropin or hepatopoietin, it was subsequently purified from the plasma of patients with fulminant hepatic failure, from rat platelets, normal human plasma, rabbit serum, and rat liver (Gohda et al., 1986; Nakamura et al., 1987; Zarnegar and Michalopoulos, 1989; Asami et al., 1991). The term "scatter factor" was introduced independently in 1985 when Stoker with co-workers discovered a protein disrupting intercellular junctions of epithelial cells, stimulating their migration in a paracrine manner, and promoting an invasive phenotype (Stoker and Perryman, 1985; Stoker et al., 1987; Weidner et al., 1990). Sequence analysis and complementary deoxyribonucleic acid (cDNA) cloning led to a conclusion that the scatter factor was indistinguishable from HGF (Gherardi and Stoker, 1990; Weidner et al., 1991). Simultaneously, various other researchers identified proteins functioning either as a growth factor for keratinocytes or an inducer of epithelial tubular formation (Rubin et al., 1989; Montesano et al., 1991a). Soon it became clear that HGF again was responsible for all the observed responses comprising growth and motility stimulations and branching morphogenesis (hence the designation of HGF as a mitogen, motogen, and morphogen) (Montesano et al., 1991b; Rubin et al., 1991).

In 1984, Cooper et al. were the first to identify the *MET* oncogene in a chemically transformed human osteosarcoma cell line by transfection analysis in NIH/3T3 cells (Cooper et al., 1984a). The oncogene, mapped to chromosome bands 7q21-31, was shown to result from a genetic translocation between two distinct loci, the *MET* proto-oncogene at chromosome 7 and translocater promoter region (TPR) at chromosome 1 (Cooper et al., 1984b; Dean et al., 1985; Park et al., 1986). The translational product of the 21-exon *MET* proto-oncogene was detected on the cell surface and classified as a growth factor receptor of the tyrosine kinase family (Gonzatti-Haces et al., 1988; Duh et al., 1997). In 1997, Schmidt et al. identified germline mutations of the *MET* proto-oncogene in hereditary papillary renal carcinoma and established a genetic link between c-MET and cancer (Schmidt et al., 1997). Subsequently, Bellusci and co-workers discovered that an autocrine loop of an otherwise unaltered HGF/c-MET pair confers oncogenic properties (Bellusci et al., 1994). These findings together with numerous reports on c-MET protein overexpression in neoplastic tissues confirmed that an aberrant activation of the c-MET cascade can be a driving force in cancer progression and onset of metastases.

Currently, a large body of evidence provides a clear rationale for specific receptor- or ligand-directed therapeutic interventions. In this respect, a number of anticancer agents, either in the form of small molecule inhibitors or monoclonal antibodies, have been tested in phase I–III clinical trials for the treatment of various malignancies including gastrointestinal, lung, brain, ovarian, and other cancers, however, without any definite overall survival benefit so far (Gherardi et al., 2012; Zhang et al., 2015).

3. Biological attributes of HGF/c-MET signalling

As mentioned above, product of the *MET* proto-oncogene acts as a transmembrane tyrosine kinase receptor for HGF (Bottaro et al., 1991; Giordano et al., 1989a,b; Park et al., 1987; Comoglio et al., 2008; Stamos et al., 2004; Basilico et al., 2008; Naldini et al., 1991; Rodrigues and Park, 1994; Ponzetto et al., 1994) (Fig. 1). The c-MET receptor is primarily located on melanocytes, endothelial cells, and epithelial tissues, including those of the liver, gastrointestinal tract, kidney, and other organs (Rubin et al., 1991; Di Renzo et al., 1991). HGF represents a multifunctional cytokine secreted as a single-chain biologically inactive precursor by fibroblasts and other elements of mesenchymal origin. The maturation occurs extracellularly where pro-HGF is cleaved into the active αβ heterodimer by urokinase type plasminogen activator (Naldini et al., 1992). The expression of HGF and c-MET is regulated by several pro-inflammatory cytokines (interleukins-1 and −6, tumour necrosis factor-alpha), p53 protein, and even HGF itself (Naldini et al., 1992; Tamura et al., 1993; Sugiyama et al., 1996; Moghul et al., 1994; Seol et al., 1999; Boccaccio et al., 1994). Activating the c-MET receptor in a paracrine manner, HGF as a peptide growth factor exerts its pleiotropic effects by controlling several transmission cascades, common to other receptor tyrosine kinases, such as the mitogen-activated protein kinase (MAPK), phosphatidylinositol-3 kinase (PI3K)/AKT, and Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathways. Nuclear factor-kappa B (NF-κB), regulating gene expression, was shown to be dependent on the c-MET-mediated recruitment of the PI3K/AKT and SRC signalling. In addition, crosstalk with epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR), or Wnt/β-catenin pathways further illustrate the complexity of intracellular c-MET networking (Gherardi et al., 2012; Trusolino et al., 2010).