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Biological, diagnostic and therapeutic relevance of the MET receptor signaling in head and neck cancer☆,☆☆

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ABSTRACT

Head and neck cancer constitutes the 6th most common malignancy worldwide and affects the crucial anatomical structures and physiological functions of the upper aerodigestive tract. Classical therapeutic strategies such as surgery and radiotherapy carry substantial toxicity and functional impairment. Moreover, the loco-regional control rates as well as overall survival still need to be improved in subgroups of patients.

The scatter-factor/hepatocyte growth factor receptor tyrosine kinase MET is an established effectors in the promotion, maintenance and progression of malignant transformation in a wide range of human malignancies, and has been gaining considerable interest in head and neck cancer over the last 15 years. Aberrant MET activation due to overexpression, mutations, tumor-stoma paracrine loops, and cooperative/redundant signaling has been shown to play prominent roles in epithelial-to-mesenchymal transition, angiogenesis, and responses to anti-cancer therapeutic modalities. Accumulating preclinical and translational evidence highly supports the increasing interest of MET as a biomarker for lymph node and distant metastases, as well as a potential marker of stratification for responses to ionizing radiation.

The relevance of MET as a therapeutic molecular target in head and neck cancer described in preclinical studies remains largely under-evaluated in clinical trials, and therefore inconclusive. Also in the context of anti-cancer targeted therapy, a large body of preclinical data suggests a central role for MET in treatment resistance towards multiple therapeutic modalities in malignancies of the head and neck region. These findings, as well as the potential use of combination therapies including MET inhibitors in these tumors, need to be further explored.

Contents

Abbreviations: *CSC*, cancer stem-like cell; *DDR*, DNA damage response; *ECM*, extracellular matrix; *EGFR*, epidermal growth factor receptor; *Egr-1*, early growth response 1; *EMT*, epithelial-to-mesenchymal transition; *FGFR*, fibroblast growth factor receptor; *HNC*, head and neck cancer; *IHC*, immunohistochemistry/immunohistochemical staining; *IL-8*, interleukin-8; *IR*, ionizing radiation; *mAb*, monoclonal antibody; *MAPK*, mutagen-activated protein kinase; *MET*, mesenchymal-to-epithelial transition receptor; *miR*, micro-RNA; *MMP*, matrix metalloproteinase; *PDGF*, platelet-derived growth factor; *PI3K*, phosphatidylinositol-3 kinase; *RPTP-β*, receptor-type protein-tyrosine phosphatase β; *RTK/TK*, receptor tyrosine kinase/tyrosine kinase; *SF/HGF*, scatter-factor/hepatocyte growth factor; *SNB*, sentinel (lymph) node biopsy; *ST-14*, suppressor of tumorigenicity-14/matriptase; *STAT*, signal transducer and activator of transcription; *TKI*, tyrosine kinase inhibitor; *VEGF(R)*, vascular endothelium growth factor (receptor).

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1. Introduction

Head and neck cancer (HNC) is the 6th most common type of cancer worldwide, with over 90% of cases arising in the mucosa of the oral cavity, the oropharynx, the larynx and the hypopharynx. Other less common locations include the nasal cavities and paranasal sinuses, the nasopharynx, the salivary glands, and the skin of the head and neck region. From a histopathological perspective, more than 90% of all cancers in the head and neck region are squamous cell carcinomas (Forastiere, Koch, Trotti, & Sidransky, 2001).

HNC has a higher incidence in men than in women, and often develops during the 5th and 6th decades of life. The main risk factors are partly dependent on the primary tumor site and include tobacco and alcohol abuse for the oral cavity, the oropharynx, the larynx, and the hypopharynx; human papillomavirus infection for oropharyngeal carcinomas; and Epstein–Barr virus infection for the nasopharynx (Gillison et al., 2008; Hashibe et al., 2009; Sankaranarayanan, Masuyer, Swaminathan, Ferlay, & Whelan, 1998).

Primary tumors arise either as premalignant lesions, such as dysplastic lesions of the oral cavity (Partridge, Emilion, Pateromichelakis, Phillips, & Langdon, 1997) or inverted papillomas of the nasal cavity and paranasal sinuses (Mendenhall et al., 2007), or as carcinomas in situ (Kowalski & Carvalho, 2000), with subsequent local infiltration and early spread to the retropharyngeal and neck lymph nodes (Leemans, Tiwari, Nauta, van der Waal, & Snow, 1993). Advanced HNC may give rise to distant metastases, mainly to the lungs and mediastinum, the liver, and the bones (Ferlito, Shaha, Silver, Rinaldo, & Mondin, 2001).

Due to their location, progression of these primary tumors can impair essential functions such as breathing and swallowing, and important features like speech and cosmesis. Furthermore, the effects that the classical treatment options for HNC inflict on the vital structures of the head and neck region cannot be overlooked. Surgical resection can indeed lead to severe impairment of the functions mentioned above. Radiotherapy and concomitant chemotherapy carry substantial skin and mucosal toxicity, and commonly lead to mucosal dryness of the oral cavity and the pharynx. More severe adverse effects of radiation include muscular and/or nervous dysfunction, soft-tissue fibrosis, osteoradionecrosis, and chondroradionecrosis. Collectively, such adverse effects can be life-lasting, making of HNC a disease with an extraordinary burden on patients' quality of life (Argiris, Karamouzis, Raben, & Ferris, 2008; Cognetti, Weber, & Lai, 2008; Gleich et al., 2003; Machtay et al., 2008).

Despite moderate improvements in loco-regional control rates, resulting from implementation of multimodal therapy approaches (such as combining surgery and chemoradiation), recurrences and distant metastases still remain devastating forms of disease, often without sufficient/effective treatment options (Argiris et al., 2008; Brockstein, 2011). Indeed, recurrent loco-regional disease or distant metastases after definitive therapy usually have a dismal prognosis since most of the patients may be offered only palliative treatment. Furthermore, even cases in which loco-regional salvage therapy (i.e., surgery and/or re-irradiation) is attempted, do not usually demonstrate a significantly improved prognosis (Specenier & Vermorken, 2008; H. K. Tan et al., 2010; Vermorken & Specenier, 2010).

HNC display substantial variety in terms of pathogenesis, progression, and treatment responses, most probably as a consequence of the complex and heterogeneous genetic and epigenetic background of these malignancies (Leemans, Braakhuis, & Brakenhoff, 2011). Increasing research efforts made in order to elucidate the molecular mechanisms of invasiveness, spread and treatment failure, have identified receptors tyrosine kinase (RTKs) as central drivers of oncogenesis in a very broad spectrum of tumors, including HNC (Elferink & Resto, 2011). As such, RTKs have gained substantial interest as therapeutic targets in clinical oncology (Elferink & Resto, 2011; Leemans et al., 2011; Molinolo et al., 2009). The idea of targeting RTKs is that, in contrast with the widely used cytotoxic drugs that are rather unspecific, critical processes which are essential and specific for disease progression would be impaired. With respect to HNC, cetuximab, a humanized anti-epidermal growth factor receptor (EGFR) monoclonal antibody (mAb), has been introduced in clinical practice after successful completion of phase III trials (Bonner et al., 2006). Besides EGFR, the mesenchymal-to-epithelial transition (MET) receptor is continuing to gain focus as a molecular target and as a relevant biomarker in HNC.

The aim of this review is to summarize currently established evidence and ongoing research concerning the biological, diagnostic, and therapeutic relevance of MET in HNC.

2. Biological aspects of mesenchymal-to-epithelial transition signaling in head and neck cancer

2.1. Molecular structure and signaling

MET is the high-affinity RTK for scatter-factor/hepatocyte growth factor (SF/HGF), its only known ligand (Bottaro et al., 1991; Goetsch, Caussanel, & Corvaia, 2013). MET is encoded by the *MET* proto-oncogene, which is located in the human 7q13 locus. *MET* is transcribed as a 6641 bp mRNA, which translates into a single 1390 amino-acid MET precursor protein (Giordano et al., 1989). This precursor is cleaved to yield the mature receptor form, which is composed of the disulfide bound α- and β-subunits. The extracellular α-subunit is highly glycosylated and contains the ligand-binding domain (SEMA domain), which shares homology with members of the semaphorin superfamily of signaling proteins. The β-subunit encompasses the juxtamembrane domain and the catalytically-active tyrosine kinase (TK) domain (Birchmeier, Birchmeier, Gherardi, & Vande Woude, 2003).

Binding of SF/HGF triggers receptor dimerization and transphosphorylation of tyrosine residues 1234 and 1235, as well as activation of tyrosine residues 1349 and 1356 within the multidocking site at the C-terminus tail of the receptor (Birchmeier et al., 2003; Giordano et al., 1989). Activation of downstream signaling effectors primarily takes place through the protein adapters growth factor receptor bound protein 2 (Grb2) and Grb2-associated binder 1 (Gab1), which consequently recruit MET targets through interaction with Src-homology-2 (SH2) and phosphotyrosine-binding (PTB) domains (Birchmeier et al., 2003).

MET activates several signaling pathways, which are also common to other RTKs (Fig. 1), primarily the mutagen-activated protein kinase (MAPK), the phosphatidylinositol-3 kinase (PI3K)-AKT, and the Janus-kinase/signal transducer and activator of transcription 3/5 (JAK-STAT3/5) pathways (Liu, Newton, & Scherle, 2010). Although multiple studies over the last two decades have identified numerous signaling components that constitute the very extensive MET signaling network, novel approaches such as post-translational modifications proteomics continue to identify new players which participate in MET-dependent signal transduction (Woodard et al., 2013).

There are two main mechanisms to terminate MET signaling. The first one consists of internalization of the receptor, with two potential outcomes: a) immediate ubiquitinization with subsequent proteasomal degradation mediated by the Cbl ubiquitin-ligase; b) maintenance of an active signaling within early endosomes, a relevant mechanism for nuclear translocation of STAT-3 and feedback activation of the MAPK pathway (Jeffers, Taylor, Weidner, Omura, & Vande Woude, 1997; Peschard et al., 2001; Scita & Di Fiore, 2010; Trusolino, Bertotti, & Comoglio, 2010).

The second regulatory mechanism is associated with activation of cellular phosphatases. MET regulatory phosphatases include protein-tyrosine phosphatase 1B, protein phosphatase 2A, T-cell phosphatase, LAR protein-tyrosine phosphatase, and density enhanced protein-tyrosine phosphatase-1 (Hashigasako, Machide,

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