Roles of the HGF/Met signaling in head and neck squamous cell carcinoma: Focus on tumor immunity (Review)

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Abstract. c-mesenchymal-epithelial transition (Met) is a transmembrane tyrosine kinase receptor of hepatocyte growth factor (HGF). HGF/Met signaling stimulates numerous pathways, including the Ras/mitogenactivated protein kinase (MAPK), phosphatidylinositol 3-kinase/protein kinase B and Wnt/β-catenin pathways, which serve important roles in cell proliferation, survival, motility, invasion and angiogenesis, and promotes the development and progression of tumors. Aberrant HGF/Met signaling is associated with a poor prognosis in several types of tumors, including head and neck squamous cell carcinoma (HNSCC). Although, the HGF/MET pathway and HGF and/or Met inhibitors have been extensively reviewed, their role in tumor immunity remains elusive. The present review article summarizes the findings on the HGF/Met signaling in HNSCC, including gene and protein alterations, biological functions and patient outcomes. Furthermore, the role of HGF/Met in tumor immunity is discussed and the controversial association between the expression of HGF/Met and the prognosis of patients with HNSCC from the perspective of tumor immunity is clarified. Ultimately, the present review proposes a clinical approach that may improve the efficacy of Met therapy for HNSCC, namely the intratumoral administration of Met inhibitors in order to reduce the inhibitory effect on immune cell recruitment. However, further studies are required to provide an improved understanding of the effects of the HGF/Met pathway on the tumor microenvironment, and the effects of HGF and Met inhibitors on immune cells in the tumor environment should be the focus of future studies.

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Contents

1. Introduction

Head and neck cancers affect the lips, oral cavity, oropharynx, nasopharynx, hypopharynx and larynx, and >836,000 new cases and 431,000 related deaths occur each year worldwide (1). Head and neck squamous cell carcinoma (HNSCC), an aggressive malignancy characterized by relatively high rates of local recurrence, low responsiveness to therapy and lymph node metastasis (2), comprises ≤90% of head and neck cancers (3). Although notable progress has been made over the past few decades in surgical, chemotherapeutic and tumor-targeting therapies for HNSCC, patient prognosis remains unsatisfactory (4). To date, the epidermal growth factor receptor-targeting biological factor cetuximab, is the only Food and Drug Administration-approved targeted therapy for HNSCC (5). However, combinatorial cetuximab treatment with radiation or chemotherapy provides only a modest benefit to survival time (29.3 vs. 49 months and 7.4 vs. 10.1 months, respectively) (6,7). Furthermore, in clinical trials, cetuximab resistance was frequently observed, along with c-mesenchymal-epithelial transition (Met) activation (8-11). Aberrant hepatocyte growth factor (HGF)/c-Met signaling has been frequently reported in HNSCC (11-14); HGF-induced Met activation is a known mechanism of cetuximab resistance (15). Therefore, given its role in HNSCC, the HGF/Met pathway may serve as a potential target for treatment of HNSCC.

Met is a transmembrane tyrosine kinase receptor (RTK) of HGF (16,17), which is structurally distinct from most other RTKs. Met consists of a 45 kDa extracellular α-chain and a 145 kDa transmembrane β-chain (18). Following binding of HGF, two Met receptors dimerize, thereby leading to phosphorylation of tyrosine residues and subsequent activation of the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt), Wnt/β-catenin, Ras/Raf and signal transducer and activator of transcription 3 pathways (19-23). By activating these pathways, HGF/Met signaling serves important physiological roles in several biological processes, including embryogenesis, wound

healing and tissue regeneration (24-27). However, during carcinogenesis, these functions promote tumor development, progression, metastasis and angiogenesis in several malignant tumors, including HNSCC (27,28). Although the HGF/Met pathway and HGF and/or Met inhibitors have been extensively studied (29-33), their roles in tumor immunity remain elusive. The present review article summarizes the current body of knowledge on HGF/Met signaling in HNSCC, including the association between gene and protein alterations, biological functions and patient outcomes. In addition, this article examines the roles of the HGF/Met signaling in tumor immunity and highlights the association between the expression of HGF/Met and prognosis of patients with HNSCC from the perspective of tumor immunity.

2. HGF/Met signaling in HNSCC

Gene and protein alterations. According to The Cancer Genome Atlas (TCGA) database, Met expression levels are significantly higher in tumors compared with normal tissues, whereas HGF expression is downregulated in HNSCC tumor tissues compared with the normal tissue (Fig. 1A) (34). HGF primarily functions as a paracrine factor in HNSCC cells. In HNSCC, HGF is primarily secreted by tumor-associated fibroblasts (TAFs) rather than the tumor cells themselves. Furthermore, it has been demonstrated that HGF is overexpressed in HNSCC-TAFs (11,35,36). Elevated HGF levels have been detected in the supernatant of TAFs cultured with laryngeal squamous cell carcinoma cells (37). Upregulated expression of Met mRNA has been frequently reported in HNSCC (12-14) . However, inconsistent with the TCGA data suggesting that the frequency of alterations in both HGF and MET in HNSCC is very low (Fig. 1B) (34), the MET mutation frequency may have been underestimated due to technical difficulties in the detection of mutations resulting in exon 14 skipping, which are in turn associated with amplification and overexpression of MET (38,39). In fact, Met protein expression is often upregulated in HNSCC tissues (40,41), and phosphorylated Met has been found to be elevated in 30% of HNSCC samples. Specifically, phosphorylation of Met at Y1003, Y1230, Y1234 and Y1235 was observed in 66% of HNSCC samples (42-44). In addition to exon 14 skipping mutations, other mutations have been identified in HNSCC tumors, including mutations in the tyrosine kinase (Y1253D, Y1230C, T1275I, V1333I, V1110I, Y1248C and R1004G), SEMA (T230M, E168D and N375S) and juxtamembrane (T1010I and R988C) domains (31,42,45). Emerging evidence has suggested that the presence of the constitutively active Y1253D Met mutant protein in primary tumors is associated with a higher risk of local tumor progression, recurrence and distant metastasis (46).

Proliferation, migration, invasion and angiogenesis. It has been shown that HGF/Met signaling promotes tumor growth, invasion and angiogenesis in several malignancies, including HNSCC (40,47,48). HGF promoted the proliferation, migration, invasion and tube formation of human lymphatic endothelial cells (35), and stimulated the growth and invasion of HNSCC cells (49,50). Furthermore, in HNSCC, HGF promoted the expression of the angiogenic factors interleukin (IL)-8, platelet-derived growth factor and vascular endothelial growth factor in tumor cells via both the mitogen-activated protein kinase and PI3K-dependent pathways (51,52). Additionally, HGF upregulated the secretion of matrix metalloproteinase-1 (MMP-1) in HNSCC cells (53). Combined inhibition of Met and FGFR significantly inhibited TAF-induced HNSCC growth both *in vitro* and *in vivo* (54). Furthermore, the Met/Akt pathway promoted epithelial-mesenchymal transition, invasion and migration of tongue squamous cell carcinoma cells (41). In oral cancer and preneoplastic cell lines, Met was activated, whereas its upregulation in oral leukoplakia was associated with a high hazard ratio for developing oral cancer (55).

Association between HGF/Met and HNSCC outcomes. The association between HGF levels and the clinicopathological parameters of HNSCC remains contested. Kim *et al* (56) demonstrated that the serum levels of HGF were significantly restored as HNSCC progressed. In addition, Uchida *et al* (57) found that the concentration of HGF in metastatic cancer tissues was significantly higher compared with that in non-metastatic tissues. However, Hong *et al* (58) suggested that in HNSCC there was no significant association between HGF serum levels and several clinicopathological parameters. Several studies have reported that Met expression is associated with various clinicopathological characteristics of patients with HNSCC, including tumor stage, tumor size and lymph node metastasis (41,59-62).

TCGA data suggested that MET upregulation was a predictor of decreased overall survival (OS, P=0.023; Fig. 1C) (34). Furthermore, the expression of HGF was a positive prognostic factor for HNSCC patient survival (P=0.024; Fig. 1C) (34), which could be attributed to the positive correlation between HGF expression and the infiltration of immune cells, including B cells and $CD4^+$ and $CD8^+$ T cells. The association between HGF/Met and tumor immunity is discussed further below. Numerous studies have supported the notion that high expression of HGF and/or MET is significantly correlated with a poor outcome (60,63-67); however, other studies have not identified such a correlation (58,68-70). Some studies demonstrated that the expression of HGF was a negative prognostic factor for the survival of HNSCC patients (63,64), whereas one study failed to reveal a correlation between HGF expression and prognosis in patients with HNSCC (58). In addition, another study demonstrated that upregulated expression of HGF had a significant effect on OS in human papillomavirus (HPV)-negative HNSCC patients, whereas no such effects on OS or progression-free survival were observed in HPV-positive HNSCC patients (71). The majority of studies have shown that high Met expression is associated with a worse outcome (60,65-67), whereas other studies have not confirmed the role of Met as a prognostic marker in patients with HNSCC (69,70).

3. HGF/Met in HNSCC tumor immunity

The immune system serves an essential role in the development of tumors (72,73). Data obtained from the Tumor Immune Estimation Resource database suggested that HGF expression was significantly positively correlated with the infiltration levels of the majority of the immune cells, including B cells, T cells, macrophages, neutrophils

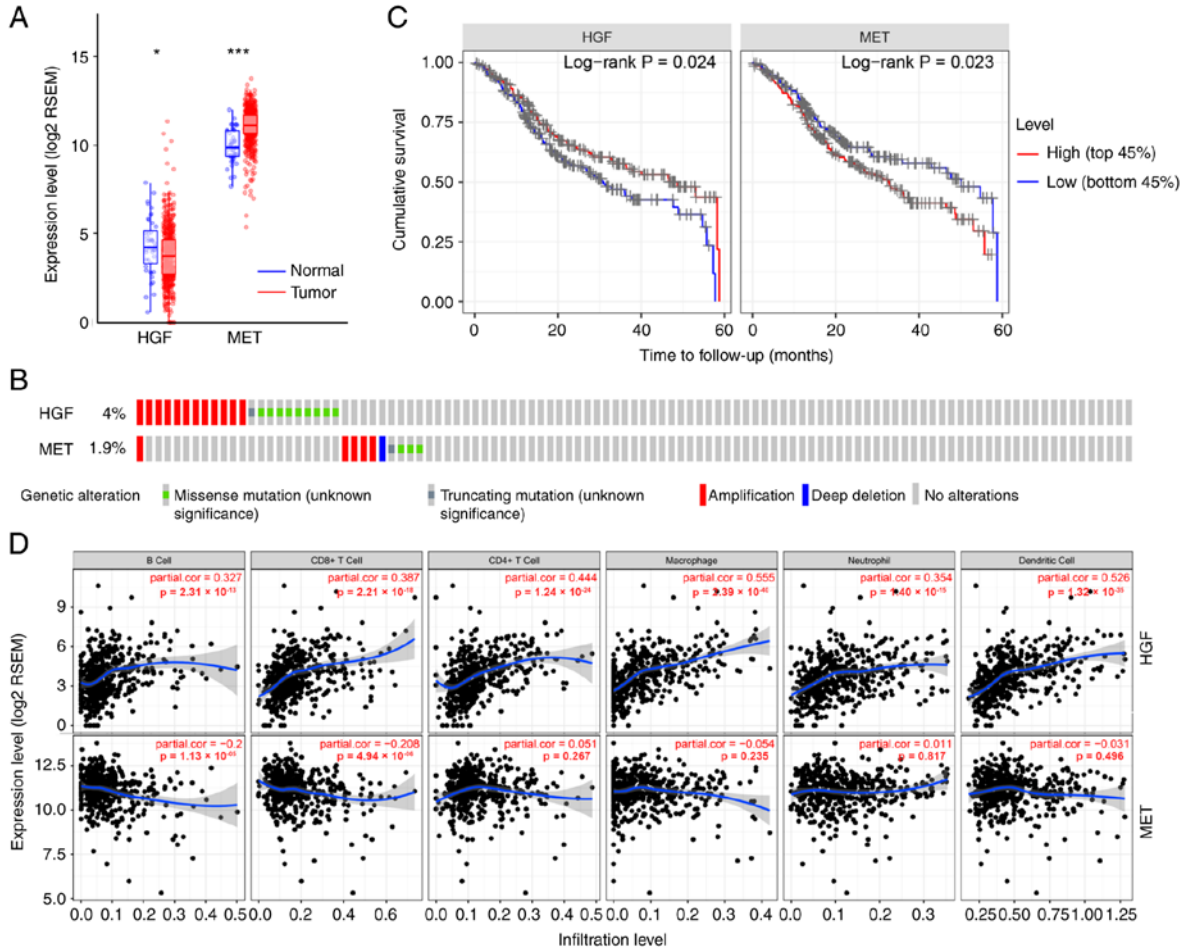

Figure 1. HGF/Met signaling in HNSCC. (A) Expression levels of HGF and MET in HNSCC tissues and normal tissues. (B) Genetic alterations of HGF/MET in HNSCC. The graph is cropped and does not show all the unaltered cases (in gray). (C) Correlation between the expression of HGF/MET and prognosis of HNSCC patients. (D) Correlation between HGF/MET expression and immune cell infiltration. HGF, hepatocyte growth factor; Met, mesenchymal-epithelial transition; HNSCC, head and neck squamous cell carcinoma; RSEM, RNA-sequence by expectation maximization.

and dendritic cells (DCs) (74,75). This finding is consistent with the chemotactic function of HGF, but not MET, and is discussed in detail below (Fig. 1D). The HGF/Met signaling pathway has been implicated in immuno-inflammation and the modulation of immune cell functions (Fig. 2) (76). It has been shown that HGF and MET are expressed in activated B cells but not in naïve B cells (77). Therefore, HGF/Met enhances B cell adhesion, migration, growth, development, survival and antibody production via mechanisms involving nuclear factor-κB and ras-related C3 botulinum toxin substrate 1 (77-83). A recent study demonstrated that tumor-infiltrating B cells may recruit $CD8^+$ T cells via CXC motif chemokine ligand 9 and maintain $CD8^+$ T cell survival in HNSCC (84). Furthermore, MET is strongly expressed in thymocytes, particularly in the $CD4^+$ $CD8^+$ double-positive subset; however, it is barely detectable in stromal cells (85). Emerging evidence has shown that HGF/Met signaling is critical for T cell lymphopoiesis, development and maturation, as well as thymocyte chemotaxis (76,77).

Neutrophils contain pro-HGF in secretory granules that can be cleaved, activated and released; therefore, *de novo* protein synthesis is not required upon cell stimulation (86). It has been reported that the treatment of chemotherapy-induced neutropenia using granulocyte-colony-stimulating factor, results in a significant increase in plasma HGF levels (87). HGF has been shown to promote the adhesion and migration of neutrophils (88). The HGF/Met axis has both pro- and anti-tumor effects in neutrophils. Neutrophil infiltration is considered as a predictor of poor prognosis in patients with bronchioloalveolar carcinoma (89). In addition, tumor neutrophils actively enhanced hepatocellular carcinoma cell metastasis both *in vitro* and *in vivo* via interactions with HGF/c-Met (90). However, in a murine model, conditional deletion of Met in neutrophils increased tumor growth and metastasis, whereas Met was also shown to be required for the recruitment of anti-tumor neutrophils (91).

Tumor-associated macrophages are involved in cancer progression and metastasis (92). HGF attenuated lipopolysaccharide-induced IL-6 production and promoted IL-10 production in macrophages, thereby reducing inflammation (87,93). Furthermore, HGF has been implicated in the recruitment of monocyte/macrophages to injured tissues and the promotion of tissue repair (94). Although HGF inhibits the differentiation of inflammatory macrophages and promotes the differentiation of anti-inflammatory macrophages, which in turn may promote HSNCC progression, the influx of monocytes, which initiates the immune response, may also inhibit HNSCC tumorigenesis (92).

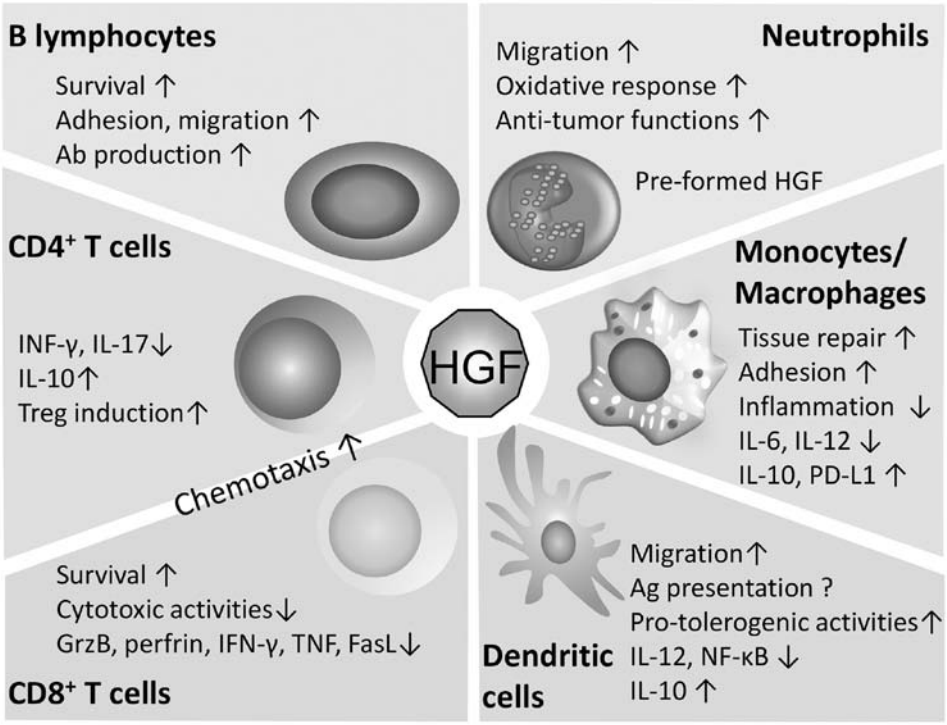

Figure 2. Effects of HGF on immune regulation. Expression of MET in immune cells is upregulated following activation. The HGF/Met signaling pathway serves an important role in the recruitment of immune cells. The HGF/Met pathway enhances B cell adhesion, migration, growth, development, survival and antibody production. HGF/Met signaling is critical for T cell lymphopoiesis, development and maturation, and thymocyte chemotaxis. Neutrophils contain pro-HGF in their secretory granules, which are cleaved, activated and released. Therefore, *de novo* protein synthesis is not required upon stimulation. HGF promotes the adhesion, migration and the anti-tumor effects of neutrophils; however, it inhibits the differentiation of inflammatory macrophages, and promotes the differentiation of anti-inflammatory macrophages. In addition, HGF/Met signaling promotes the adhesion, migration and the pro-tolerogenic activities of DCs. HGF, hepatocyte growth factor; Met, mesenchymal-epithelial transition; DCs, dendritic cells; IL, interleukin; INF-γ, interferon-γ; TNF, tumor-necrosis factor; FasL, Fas ligand; PD-L1; NF-κB, nuclear factor-κB; Treg, regulatory T-cell; Ag, antigen; Ab, antibody; GrzB, granzyme B.

DCs serve key roles in both innate and adaptive immune responses (95,96), and several studies have shown that HGF/Met signaling promotes the adhesion and migration of DCs (97,98). However, the effect of HGF on the antigen-presenting ability of DCs remains controversial. Benkhoucha *et al* (99) and other studies (77,97) demonstrated that neither HGF nor ablation of MET affects the ability of DCs to present antigenic peptides to $CD4^+$ T cells and induce the expansion of regulatory T cells. In contrast, another study using a murine model showed that HGF inhibited antigen presentation by DCs (100). Additionally, PI3K-dependent activation of Met upregulated PD-L1 expression in renal, gastric, liver and non-small cell lung cancer cells (101-104). However, the PI3K pathway is often mutated and activated in HNSCC (105). Increased Met expression was significantly associated with decreased PD-L1 expression (P=0.010) in HNSCC (67), indicating that there may be another regulatory mechanism between Met and PD-L1 in HNSCC, and combined blockade of Met and PD-L1 could exert mutually reinforcing effects.

In summary, it is hypothesized that the positive correlation between the expression of HGF and immune cell infiltration in HNSCC may be associated with the inhibition of tumorigenesis and may support the notion that HGF overexpression predicts increased OS. However, additional evidence is required to support this hypothesis. Therefore, it is hypothesized that targeting Met and particularly HGF for treatment of HNSCC may compromise several functions of anti-tumor immune cells. Thus, clinical trials using HGF or Met inhibitors for HNSCC therapy should be cautiously evaluated.

4. Conclusion

Due to its crucial role in cancer cell proliferation, invasion and metastasis, HGF/Met signaling is an attractive target for the treatment of HNSCC. The present review summarizes the current body of knowledge of the role of HGF/Met signaling in HNSCC, including gene and protein alterations, biological functions, patient outcomes and tumor-immune system interactions. Given that patients with tumors exhibiting high-level MET amplification or MET exon 14-skipping variants are more likely to benefit from anti-Met therapies (29), the detection of MET alterations is necessary for assessing whether to use Met inhibitors to treat HNSCC. Several researchers have hypothesized that HGF is a promising therapeutic target for HNSCC treatment. However, given the impact of the HGF/Met signaling in the recruitment of immune cells, the association between the expression of HGF and HNSCC outcomes, and the early termination of a phase III study combining an HGF antibody (rilotumumab) with chemotherapy due to the increased number of deaths in the rilotumumab arm vs. that in the placebo arm (106), it is hypothesized that inhibition of HGF could attenuate several anti-tumor immune responses. Therefore, intratumoral administration of HGF inhibitors may not be a suitable approach for the treatment of HNSCC. Ultimately, a clinical approach that may improve the efficacy

of Met therapy for HNSCC, namely, intratumoral administration of Met inhibitors in order to reduce the inhibitory effect on immune cell recruitment may instead improve patient outcomes. However, further studies are required to provide an improved understanding of the effects of the HGF/Met pathway on the tumor microenvironment and to evaluate the therapeutic value of targeting HGF/Met in HNSCC. In addition, given the important role of HGF/Met signaling on immune cells, it is necessary to study the effects of HGF and Met inhibitors on immune cells in the tumor environment; however, to the best of our knowledge, no studies have assessed this at present. Therefore, the effects of HGF and Met inhibitors on immune cells in the tumor environment should be the focus of future studies and clinical trials using HGF or Met inhibitors for HNSCC therapy should be cautiously evaluated.

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Authors' contributions

DL collected data and wrote the manuscript. MZ, DZ and YZ collected data. SL drew figures and edited the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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