HGF and c-MET as potential orchestrators of invasive growth in head and neck squamous cell carcinoma

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1. ABSTRACT

Head and neck squamous cell carcinoma (HNSCC) constitutes 90% of all head and neck cancers and is associated with high mortality rates, due to the high infiltrative potential of these tumors. Despite advances in treatment approaches, there has been no improvement in survival rates. As empiricism in the treatment of HNSCC is unlikely to improve the prognosis of HNSCC patients, understanding the pathogenesis behind the local invasion of these tumors on the cellular and molecular levels has become an important goal in the field of head and neck surgery. It is believed that the invasive growth of neoplastic cells is a deregulated form of the physiological program that occurs during the formation and patterning of an embryo, which is largely facilitated by HGF induced signaling through its receptor c-MET. This review investigates whether HGF and c-MET are deregulated in HNSCC and whether they confer an invasive potential to these tumors. It is concluded that both molecules are mis- and over-expressed in HNSCC and probably induce the program of invasive growth in HNSCC.

2. INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) constitutes 90% of all head and neck cancers (1). It is the fifth most common type of cancer in men with approximately 780,000 new cases worldwide every year (2). It is associated with high mortality rates as about one half of all individuals diagnosed with HNSCC will not survive to the five year mark (3, 4). The poor survival rate for patients with HNSCC is due to the high infiltrative potential of the tumors that can result in early regional lymph node involvement and subsequent metastatic spread, in addition to a high rate of recurrence and a high risk of secondary malignancies (5).

Despite advances in aggressive and multidisciplinary treatment approaches, including preoperative or postoperative chemotherapy and/or radiotherapy with reconstructive surgery, there has been no evidence over the past 20 years to suggest any significant improvement in the 5-year survival rate (6). As current treatment strategies relying on clinical, radiologic, and
Increased HGF expression has indeed been significantly linked with lymph node metastasis (14-17). Unfortunately, the corresponding results for c-MET are
inconsistent. Where one expression study showed no correlation between c-MET’s expression and lymph node status (16), three other studies did identify a significant correlation between c-MET over-expression and lymph node status (14, 18, 19, 21). After taking into consideration that mutated c-MET expands clonally to the lymph node and that c-MET is frequently detected at high expression levels in affected lymph nodes and is always absent in unaffected lymph nodes (18), it is concluded here that in vivo the HGF/c-MET receptor tyrosine kinase system is associated with the invasive potential of HNSCCs. This has been confirmed in vitro by analyzing the invasive behavior of HGF stimulated, c-MET positive HNSCC cell lines by means of invasion assays (23, 24).

Under normal physiological conditions, c-MET activation is a transient event. In cancerous tissues, however, c-MET is often constitutively activated. This deregulated mode of activation can be due to different molecular alterations; these include ligand-independent receptor oligomerization and activation due to c-MET over-expression, point mutations in c-MET’s tyrosine kinase domain that render this receptor constitutively active, and HGF-dependent autocrine and/or paracrine receptor activation (25), all of which can plausibly occur in HNSCC.

4. HGF AND c-MET AS ORCHESTRATORS OF INVASIVE GROWTH IN HNSCC

As already mentioned in the introduction, invasive growth is a multi-step program; there are four major steps: cellular detachment, proteolytic degradation of the basal lamina, migration through the ECM, and resistance to apoptosis in an unfamiliar environment (9). Over the past three decades, several experiments have shown that HGF promotes each of these steps in HNSCC cell lines (17, 23, 26-30). This chapter will clarify the precise molecular mechanisms the HGF/c-MET receptor tyrosine kinase system uses during the progression of HNSCC.

4.1. Detachment of carcinoma cells from their primary tumor mass

Under normal growth conditions, cuboidal epithelial cells associate into tight, polarized sheets by adhering to each other through regularly spaced cell-cell junctions (31, 32). This implies that neoplastic epithelial cells must overcome these physical constraints if they are to move away from their primary tumor mass.

Most carcinomas, including HNSCCs (for a review, see ref. (36)), transcriptional repression in particular emerges as a fundamental mechanism for the dynamic silencing of E-cadherin during tumor progression (37).

In 2001, Yokoyama et al. (38) discovered an inverse correlation between the expression of Snail – a direct transcriptional repressor of E-cadherin (39) – and E-cadherin in oral SCC cells in vitro. While this indicated that E-cadherin is transcriptionally repressed in HNSCC, the underlying molecular mechanism remains unknown. Only recently, Grotegut et al. (26) have discovered that HGF probably induces the expression of early response growth factor-1 (Egr1) through MAPK signaling in epithelial cell lines and subsequently showed that Egr1 in its turn acts as a direct transcriptional activator of Snail. This, in combination with an observed decrease of E-cadherin mRNA in a HGF treated hypopharyngeal squamous cell carcinoma (SCC) cell line (17), suggests that HGF is a potential orchestrator of Snail-induced repression of E-cadherin in HNSCC. Nevertheless, the observation of Williams et al. (40) that E-cadherin staining increases in the cytoplasm before normal linear membranous staining is breached during oral carcinogenesis, suggests that other molecular mechanisms besides transcriptional repression are involved in the deregulation of E-cadherin in HNSCC.

Approximately 2 decades ago, Crepaldi et al. (41) found that the c-MET receptor localizes, in vivo as well as in vitro, at the basolateral surfaces of epithelial cells and shows a staining pattern that is quite similar to that of E-cadherin. This apparent co-localization of c-MET and E-cadherin was confirmed in vitro by two independent studies (42, 43); the second of these suggested that E-cadherin stabilizes c-MET’s position in the cell membrane in a variety of epithelial cancer cell lines through an interaction between the extracellular domains of these two proteins. Additionally, both studies pointed out that c-MET as well as E-cadherin disappear from adherens junctions in response to HGF. More specifically, the first study revealed that c-MET and E-cadherin disappeared from the membrane and accumulated in the perinuclear area with almost identical time courses in cultured wild type MDCK cells treated with HGF. This implies that these two proteins undergo co-endocytosis in response to HGF. It is therefore argued here that this receptor/cadherin pairing may be a mechanism to optimize the concomitant translocation of c-MET and E-cadherin from the membrane to the cytoplasm in response to HGF. Also in cultured HNSCC cell lines, c-MET and E-cadherin were seen to co-localize (17, 24) and associate at intercellular junctions (24) that were disrupted after stimulation with HGF by translocation of E-cadherin from the membrane to the cytoplasm (17). Furthermore, when comparing HGF expression to membranous or cytoplasmic expression of E-cadherin in human hypopharyngeal SCC specimens, the expression of HGF was found to be significantly higher in the group with cytoplasmic expression of E-cadherin than in the group with membranous expression of E-cadherin (17). In primary HNSCC tissue samples the staining pattern of c-MET, like that of E-cadherin, emerges as membranous and/or cytoplasmic (14, 18, 19) in contrast to its strictly membranous staining pattern in normal mucosa (21). In
HGF/c-MET regulated invasiveness of HNSCC

Figure 1. HGF/c-MET facilitated detachment of neoplastic cells from primary HNSCCs through MAPK signaling, which results in Snail mediated transcriptional down-regulation of E-cadherin.

Because the introduction of HGF to cultured HNSCC cell lines (17, 44) creates a picture of cellular dissociation similar to that of adding a neutralizing E-cadherin anti-body to a cultured HNSCC cell line (17), it may be concluded that HGF most likely facilitates the detachment of neoplastic cells from their primary tumor mass by Snail- induced transcriptional down-regulation of E-cadherin (Figure 1) and the endocytosis of an E-cadherin-c-MET complex in HNSCC.

4.2. Epithelial mesenchymal transition during invasive growth

Historically, two distinct cell lineages have been identified on the basis of their shape and the organization of the multi-cellular structures they create. As already mentioned, cuboidal epithelial cells associate into tightly polarized sheets by adhering to each other through E-cadherin. This tissue architecture inhibits individual cell movement. In contrast, irregularly shaped mesenchymal cells do not organize themselves in regimented structures nor exhibit tight intracellular adhesion, and this lack of regular cellular organization promotes cell migration (31, 32). Although it has been known for a long time that these cell types interconvert during embryonic development in processes referred to as epithelial-mesenchymal transition (EMT) and mesenchymal-epithelial transition (MET), EMT has only recently been recognized as a potential mechanism in facilitating the progression of a carcinoma by conferring an invasive phenotype to neoplastic cells (45).

EMT is defined as a process by which epithelial cells acquire a fibroblastoid phenotype, down-regulate epithelial-specific proteins, induce various mesenchymal proteins, and digest and migrate through the ECM (46). Despite increasing evidence for the involvement of EMT in tumor progression, the topic remains controversial as the great diversity of cellular organization in human tumors makes it impossible to recognize EMT definitively (45). The first growth factor known to induce EMT in vitro was HGF, and it is therefore being investigated here whether HGF facilitates EMT in HNSCC.

E-cadherin’s transcriptional repressor, Snail, may play a key role in mammalian EMTs as, its transcript can be found in the regions that undergo EMT during the development of mouse embryos. Additionally, its ectopic over-expression induces a complete EMT – as defined above – in cultured epithelial MDCK cells, involving the repression of the epithelial marker E-cadherin and the induction of the mesenchymal markers vimentin and fibronectin, as well as the acquisition of invasive and migratory properties (39). Additionally, Yokoyama et al. (38, 47) have observed that E-cadherin positive oral SCC cell lines do not express Snail, exhibit normal cuboidal morphology with extensive cell-cell adhesions, and have no invasive capabilities. In contrast, he also observed that E-cadherin negative oral SCC cell lines exhibit fibroblastic morphologies, express vimentin, and possess invasive capabilities, suggesting that the expression of Snail in oral SCC cell lines induces a full EMT. This was confirmed by the loss of E-cadherin, epithelial cell morphology, and the increased invasiveness after transfection of Snail in the E-cadherin positive oral SCC cell lines.

After taking all the findings into consideration, it is assumed here that the HGF/c-MET receptor tyrosine kinase system facilitates invasive growth in HNSCC by inducing a program similar to EMT. Whereas the preceding subchapter has already discussed the mechanisms that HGF uses to initiate loss of E-cadherin expression, the following two chapters will focus on the mechanisms used to mediate invasion and migration through the ECM.

4.3. Induction of proteolytic cleavage of the basal lamina

In addition to adhering to each other, healthy epithelial cells attach to a specialized form of the ECM, called the basal lamina, which separates them from the underlying connective tissue (48). Once dissociated from their primary tumor mass, cancer cells must break through this structure before they are capable of migrating through
HGF/c-MET regulated invasiveness of HNSCC

**Figure 2.** HGF/c-MET induced expression of MMPs through Snail and E1AF, which facilitates proteolytic degradation of the ECM in HNSCC.

The interstitial matrix (IM) – the ECM that resides in connective tissue. In fact, disruption of the integrity of the basal lamina is a key histological marker for the transition from an *in situ* to an invasive carcinoma (48). Local degradation of the ECM requires the expression of specific proteases. The matrix metalloproteinases (MMPs) are the main family of proteases known to be involved in the remodeling of the ECM. They are synthesized as inactive pro-enzymes and then converted to active enzymes through the proteolytic removal of an autoinhibitory domain (49). The expression and activity of MMPs are increased in almost every type of human cancer (for a review, see ref. (50)), including HNSCC (for a review, see ref. (5, 7, 51)). It has been discovered that a transcription factor of the Ets family, E1AF, up-regulates the promoter activities of MMP1, MMP3, MMP9, and MMP14 (52, 53). Further investigation (54) has revealed a direct correlation between the expression levels of E1AF mRNA and MMP1 as well as MMP9 protein, which were all high in invasive and low in non-invasive oral SCC cell lines. An additional *in situ* hybridization located E1AF mRNA at the invasive front of oral SCC cells seeded on a collagen gel (54). Furthermore, a highly invasive oral SCC cell line was observed to lose its invasive potential and expression of MMP1, MMP3, and MMP9 after stable transfection with anti-sense E1AF (55). Finally, the same invasive oral SCC cell line was demonstrated to induce the expression of E1AF, MMP1, MMP3, and MMP9 and to undergo an increase in invasive potential after treatment with HGF.

Additional analyses of some of these responses to HGF, specifically MMP9 expression and invasiveness, revealed that they were counteracted by anti-sense E1AF and an MMP9 promoter that lacks the Ets-binding site (23). All these results imply that E1AF confers invasive properties to oral SCC cell lines by initiating the expression of MMPs in response to HGF.

In oral SCC tissue specimens, E1AF expression was more frequent in metastasizing samples and significantly linked with their invasive behavior (56). Additionally, a significant correlation was found between the expression of E1AF and the expression of MMP14 in a set of tongue SCCs that tended to metastasize (53). These observations suggest that the E1AF-mediated expression of MMPs also confers invasive properties to oral SCCs *in vivo*.

While the possibility that other Ets family members might respond to HGF stimulation cannot be excluded, it is concluded here that HGF confers invasive properties to HNSCCs by inducing E1AF regulated expression of MMPs (Figure 2).

In addition to the MMPs discussed in the previous paragraph, there is another MMP frequently used by tumors to enhance their invasive potential, namely MMP2 (50). Although Izumiyama *et al.* (53) have proven that E1AF has no effect on the expression of MMP2, Bennett *et al.* have seen that HGF is capable of stimulating MMP2 expression *in vitro* in both normal and malignant human oral mucosal keratinocytes. In 2003, Yokoyama *et al.* (47) discovered that the transcription factor Snail acts as a transcriptional regulator of MMP2 and an enhancer of invasiveness in a non-invasive oral SCC cell line. Keeping in mind that HGF induces the expression of Snail through Egr1, it is fair to suggest here that HGF may enhance the invasiveness of HNSCCs through Snail orchestrated expression of MMP2 (Figure 2). Further research, however, is needed to determine whether Snail directly activates the promoter of MMP2 or uses a set of co-activators instead.

In addition to its function as a tissue barrier, the ECM is used by cells as a substrate for many activities, including cellular migration (49, 57). Therefore, during tumor progression, proteolysis of the ECM must be carefully controlled to the point where the ECM is sufficiently degraded to facilitate cell passage, but not so degraded that cellular traction is lost (48).

### 4.4. Promotion of migration through the extracellular matrix

Mesenchymal migration through tissues is the result of a continuous cycle of interdependent steps. First, a migrating cell forms protrusions, called filopodia, in the direction of its movement. Eventually these filopodia make contact with the ECM where they merge into a lamellipodium, which in turn mediates the attachment to its substrate through integrins, a diverse family of glycoproteins that form heterodimeric transmembrane receptors for ECM molecules. Next, regions of the cell’s leading edge or its entire cell body contract, while older
adhesion complexes at its trailing edge are disassembled, allowing the gradual forward gliding of the cell body and its rear end (48, 49, 57, 58).

As described above, a cell body must change its shape and degree of stiffness in order to initiate and maintain cell motility. Moreover, it has been established that during physiological cell migration, a specific group of proteins regulate these changes in cell morphology, namely the RHO family of small GTPases, whose prototypic members include RHOA, RAC1, and CDC42. Like Ras, the RHO GTPases can cycle between their inactive GDP- and active GTP-bound states. The exchange of GDP with GTP is promoted by activated growth factor receptors as well as integrins and is often associated with the translocation of RHO GTPases from the cytoplasm to the membrane. Whereas CDC42 is important for the formation of filopodia and RAC1 induces the formation of lamellipodia, RHOA is involved in the generation of actin stress fibers and focal adhesions (48, 59).

Following ligand binding, integrins cluster in the cell’s lamellipodium, forming focal adhesions. Focal adhesions are structures rich with actin-associated proteins — such as alpha-actinin, vinculin, tensin, and paxillin — and signaling molecules. One of these signaling molecules is the focal adhesion kinase (FAK), which becomes tyrosine phosphorylated upon integrin engagement and sometimes upon growth factor receptor activation. FAK autophosphorylation creates a high-affinity binding site for the tyrosine kinase c-SRC. After binding, c-SRC phosphorylates FAK on additional tyrosine residues, leading to FAK’s full enzymatic activity. Subsequently, FAK induces a complex network of signaling pathways that includes the signaling molecule ERK. In its turn, ERK controls cell locomotion by generating contractile forces that pull the cell forward (48, 57, 60).

In 1994, Matsumoto et al. (27) found that HGF markedly stimulated the migratory capacity of an oral SCC cell line that was plated on a collagen type I matrix in a biphasic manner. Almost immediately after treating this cell line with HGF, there was a rapid increase in cell spreading, along with the formation of focal adhesion containing integrin-beta1, FAK, and vinculin. After a certain amount of time, however, these cells gradually lost their focal adhesions and cell-cell contacts, took on a motile, spindle-shaped morphology, and exhibited increased locomotion. Furthermore, an increase in tyrosine phosphorylation of c-MET and FAK could be observed shortly after treatment with HGF. While these observations suggest that activation of c-MET induces the phosphorylation of FAK, the possibility does exist that phosphorylation of FAK is not HGF-specific, as it was also induced by EGF. Several years later, Kitajo et al. (28) discovered that HGF stimulation of another oral SCC cell line triggered the activity of RHOA, which subsequently acted as an upstream mediator of FAK as the inhibition of RHOA prohibited the phosphorylation of FAK in addition to cell migration. Both experiments indicated that phosphorylation of FAK is important for the induction of cell migration; however, the mechanism that is responsible for this action remains elusive. Around the same time as Kitajo, Crowe et al. (61) found that, in a SCC cell line, FAK associates with integrin-beta1 upon attachment to collagen type IV and that this complex formation is necessary for the induction of cellular migration on collagen type IV. Additionally, it was pointed out that FAK-dependent cellular migration over collagen type IV required the activity of ERK.

After taking all factors into consideration, it is speculated here that HGF may indeed facilitate migration in vitro in oral SCC cells by mediating a transition from an epithelial to a fibroelastic morphology through the activation of the RHO GTPases upon ligation to c-MET, which in turn leads to the formation of focal adhesions and changes in cell shape (Figure 3A). Next, during the formation of focal adhesion, FAK becomes autophosphorylated, eventually leading to the activation of ERK. Finally, ERK induces cellular contraction and the down-regulation of E-cadherin through Snail (Figure 3B).

4.5. Inhibition of anoikis

As described above, efficient tumor invasion requires the local degradation of the basal lamina as well as the partial degradation of the IM, which results in inappropriate adhesion to the ECM. Since loss of attachment to the ECM triggers a specialized form of apoptosis — known as anoikis — in normal epithelial cells (62), resistance of invasive tumor cells to anoikis is crucial to the successful execution of invasive growth.

Zeng et al. (29) found that HGF protected various HNSCC cell lines — when placed in suspension — from anoikis by signaling through both ERK and Akt, as inhibition of either ERK or Akt activation was sufficient to abolish HGF-mediated survival. Because activation of the dimeric AP-1 transcription factor — composed of JUN and FOS family members — involves the ERK signaling pathway (63, 64), further analyses were performed to investigate whether AP-1 contributes to HGF-mediated survival in HNSCC in vitro (30). The observation that c-Fos mRNA was increased in a HGF treated HNSCC cell
line and that stable transfection of the same cell line with TAM67 – a dominant negative mutant of c-Jun – showed no resistance to anoikis after the addition of HGF, confirmed the hypothesis that HGF-mediated cell survival through ERK in HNSCC involves AP-1 in vitro. Finally, the anti-apoptotic Cox-2 gene was found to be up-regulated in response to HGF in the last mentioned HNSCC cell line. Nevertheless, it is suspected that several additional anti-apoptotic genes are induced by HGF as the protective level of over-expressed Cox-2 against anoikis in vitro was weaker than that of HGF. These findings suggest that HGF may offer HNSCCs resistance to anoikis in vivo by inducing gene expression of Cox-2 through AP-1 (Figure 4).

5. PERSPECTIVE

Although, to our knowledge, this is the first review to elaborate on the role of the HGF/c-MET receptor tyrosine kinase system in the invasive growth of HNSCCs, it represents only the beginning of the story.

Dissemination of cancer cells to lymph nodes and/or remote tissues involves more than invasive growth. In fact, before invasive growth even takes place, tumor cells grow progressively (progressive growth) and induce the formation of new blood vessels (angiogenesis). Furthermore, in order to reach lymph nodes and/or distant sites, invasive cells must penetrate blood and/or lymphatic vessels (intravasation), survive in the circulatory system (survival in transit), become trapped in lymph nodes and/or capillary beds of distant organs (arrest), exit the circulatory system (extravasation), and colonize distant sites (progressive growth) (49, 65, 66). Note that the latter two requirements are specific to the completion of distant metastasis.

Using the mechanisms described in chapter 4, the HGF/c-MET tyrosine kinase system may facilitate several steps of the metastatic process in addition to invasive growth, including progressive growth through resistance to apoptosis, intravasation and extravasation through the production of MMPs, and survival in transit through anoikis.

Additionally, HGF may facilitate angiogenesis in HNSCC as the addition of HGF to a set of HNSCC cell lines has been shown to increase their production of several pro-angiogenic factors, such as IL8, VEGF, and PDGFA (67, 68).

The preceding paragraph illustrates that the HGF/c-MET tyrosine kinase system is intimately involved in the metastasis of HNSCC. Since c-MET is already a target in the development of cancer therapies in general (10, 25, 69), this kinase may offer new possibilities in the treatment of HNSCC patients.

As metastasis to cervical lymph nodes is a major determinant of patient outcome in HNSCC (70) and the diagnostic assessment of the lymph node status of the neck is not reliable (71), features that predict the presence of lymph node metastases may be useful to assess prognosis more precisely in patients with HNSCC. In 1997 (72) and 2002 (71) Takes et al. investigated whether there are markers that predict the presence of metastasis based on features of the primary tumor. They found that several histopathological features and the expression of some molecular markers – e.g. loss of E-cadherin – indeed supplied some information on the metastatic behavior of tumors. Incorporating this type of information in prognostic models, similar to the one mentioned in the introduction, might improve the assessment of a patient’s prognosis. Since the expression of both HGF and c-MET increases during progression of HNSCC and is associated with lymph node status, both molecules might serve as prognostic markers in HNSCC.

This review is written from the perspective that ligation of HGF to c-MET is sufficient to activate all the signaling pathways discussed in chapter 4. However, it has now been well established that receptor tyrosine kinase activation is more complex in the sense that these types of receptors generally are associated with several proteins that affect their activation. In particular, proteins which lack a kinase domain, so-called co-receptors, cooperate with receptor tyrosine kinases by modulating their kinase activity.
activity (73). Also, c-MET is known to cooperate with several co-receptors, namely CD44v6, integrin α6β4, and plexinB1 (74). The fact that CD44v6 is associated with HNSCC (75) offers an interesting opportunity for future research into HNSCC. For instance, one might explore to what extent these molecules cooperate during the progression of HNSCC.

6. CONCLUSION

Both HGF and its receptor, c-MET, are mis- and over-expressed in HNSCC; this situation may lead to the constitutive activation of the receptor tyrosine kinase system. This aberrant activity most likely induces the program of invasive growth by conferring an invasive potential to these tumors.

As with physiological conditions, HGF and c-MET orchestrate invasive growth during the progression of HNSCC by integrating several independent biological responses using a specific set of signaling pathways.

Specifically, HGF/c-MET may facilitate the detachment of neoplastic cells from primary HNSCCs through MAPK signaling, which may result in the Snail-mediated transcriptional down-regulation of E-cadherin. Additionally, HGF/c-MET may allow HNSCC cells to break through their basal lamina by inducing E1A and Snail-regulated expression of MMPs. Furthermore, HGF/c-MET may promote migration by changing the non-motile epithelial morphology of invasive HNSCC cells into a motile fibroblastic morphology through the utilization of the RHO GTPases. During transformation, FAK probably becomes activated, and this induces cell locomotion through ERK. Also, HGF/c-MET may up-regulate the anti-apoptotic gene Cox-2 through AP-1, which lies downstream of ERK. Besides ERK signaling, AKT signaling may inhibit anoikis in HNSCC.

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