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Molecular parameters of head and neck cancer metastasis

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Abstract

Metastasis remains a major cause of mortality in patients with head and neck squamous cell carcinoma (HNSCC). HNSCC patients with metastatic disease have extremely poor prognosis with survival rate of less than a year. Metastasis is an intricate sequential process which requires a discrete population of tumor cells to possess the capacity to intravasate from the primary tumor into systemic circulation, survive in circulation, extravasate at a distant site, and proliferate in a foreign hostile environment. Literature has accumulated to provide mechanistic insight into several signal transduction pathways, receptor tyrosine kinases (RTKs), signal transducer and activator of transcription 3 (Stat3), Rho GTPases, protein kinase Cε (PKCε), and nuclear factor-κB (NF-κB), that are involved in mediating a metastatic tumor cell phenotype in HNSCC. Here we highlight accrued information regarding the key molecular parameters of HNSCC metastasis.

Keywords

HNSCC; squamous cell carcinoma; migration; invasion

I. Introduction

Approximately 600,000 new cases of head and neck squamous cell carcinoma (HNSCC) are diagnosed worldwide each year.[1-3] In the United States, it is estimated that HNSCC will account for 45,660 new cases and 11,210 deaths in 2007.[4] HNSCC is divided into three general clinical categories; early-stage disease (Stage I/II), locally advanced disease (Stages III/IV), and recurrent/metastatic disease. Curative treatment is often achieved in patients presented with early-stage disease through surgery or radiation. Palliative chemotherapy is the standard approach for patients with recurrent/metastatic disease. The majority, greater than two-thirds, of HNSCC patients present with locally advanced disease that requires a modern multi-disciplinary approach involving surgery, radiation, and pharmacotherapy. A majority of patients with locally advanced HNSCC treated with chemoradiation or surgery have initial locoregional control but will eventually develop recurrence and/or metastasis. In fact, distant metastasis is more prevalent now due to better locoregional control with multi-

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modality treatment regimens. Unfortunately, limited therapeutic options are available for HNSCC patients with recurrent/metastatic disease. Palliative chemotherapy is effective in only about one-third of these patients. Patients that do not respond to palliative chemotherapy or progress during palliative chemotherapy have no effective recourse. The median overall survival for HNSCC patients with recurrent/metastatic disease is a dismal 5 to 9 months.[5, 6] Thus, there is a critical need to understand the genetic determinants of metastatic HNSCC to allow for better clinical management.

Metastasis is an intricate process involving a cadre of genes resulting in reprogramming of a discrete population of tumor cells within the primary tumor. Metastatic tumor cells must possess the capacity to intravasate from the primary tumor into systemic circulation, survive in circulation, extravasate at a distant site, and proliferate in a foreign hostile environment. Numerous cellular processes, including apoptosis, invasion, and migration, are required to be co-opted by metastatic tumor cells in order to successfully establish metastatic disease. Receptor tyrosine kinases, epidermal growth factor receptor (EGFR), TrkB and c-Met, signal transducer and activator of transcription 3 (Stat3), Rho GTPases, protein kinase Cε (PKCε), and nuclear factor-κB (NF-κB) are implicated to modulate different aspects of cellular events necessary to induce metastasis in HNSCC. This review highlights published work on the role of these key genes in driving a metastatic tumor cell phenotype in HNSCC. Understanding the molecular parameters of metastatic HNSCC will be necessary to improve on the detection and treatment approaches for aggressive HNSCC.

II. Receptor tyrosine kinases

Epidermal growth factor receptor (EGFR) is a member of the ErbB/Her family of receptor tyrosine kinase (RTK) which also includes Her2, Her3 and Her4. The epidermal growth factor (EGF) and transforming growth factorα (TGFα) are the main ligands which bind to EGFR. Ligand binding induces a conformational change causing EGFR to homodimerize or heterodimerize with other members of the Her family leading to autophosphorylation and activation of the intrinsic tyrosine kinase to initiate downstream signaling. EGFR have been reported to activate ras-mitogen activated protein kinase kinase (MEK), extracellular signal regulated kinase (ERK), phosphatidylinositol-3-kinase (PI3K)-Akt, c-Src, Stat3, c-Met, and phospholipase Cγ-1 (PLCγ-1).[7-11]

A recent report demonstrated that EGF induced epithelial-to-mesenchymal (EMT) transition in SCC10A cells with a decrease in E-cadherin levels and an increase in N-cadherin and vimentin levels.[12] SCC10A cells were highly invasive and motile in response to EGF treatment. Additionally, over-expression of E-cadherin was sufficient to blunt EGF-mediated cell invasion and migration. EGFR also has been demonstrated to prevent anoikis, programmed cell death of non-attached cells, in HNSCC cells. Upon detachment from the extracellular matrix, contact with neighboring HNSCC cells activates an EGFR-E-cadherin complex which activates ERK and increased the levels of anti-apoptotic protein Bcl2.[13] EGFR contributes to a metastatic HNSCC tumor cell phenotype through regulation of invasion, migration, and anoikis. EGFR has been reported to modulate cell invasion through activation of PLCγ-1 and c-Src.[9, 14] EGF stimulation resulted in an increase in PLCγ-1 phosphorylation and activity in HNSCC cell lines.[9] Pharmacological inhibition of EGFR blunted EGF-stimulated PLCγ-1 activation. Moreover, cell invasion was impaired in HNSCC treated with PLCγ-1 antisense. HNSCC treated with EGF enhanced the binding interaction between c-Src and EGFR.[15] It was shown that gefitinib, an EGFR tyrosine kinase inhibitor, suppressed c-Src activation and invasion in HNSCC.[16] Over-expression of constitutive active c-Src enhanced cell invasion in 1483 HNSCC cells.[17] Additionally, inhibition of c-Src and EGFR, using small molecule inhibitors, AZD0530 and gefitinib,

dramatically blunted invasion in PCI-37B and 1483 cells.[17] Lastly, combined inhibition of PLCγ-1 and c-Src further attenuated cell invasion in HNSCC cells.[18]

EGFR variant III (EGFRvIII) is the most common truncated form of EGFR. EGFRvIII has an in-frame deletion of exons 2 to 7 resulting in a truncated extracellular domain.[19, 20] This deletion alters the conformation of EGFR resulting in a ligand-independent, constitutively active EGFR. EGFRvIII has been reported to be expressed in 40% of HNSCC tumors and has been linked to tumorigenesis and metastasis.[21] Expression of EGFRvIII in wildtype EGFR expressing HNSCC cells enhances cell proliferation, migration, invasion and *in vivo* tumor growth.[22] Tumor xenografts from EGFRvIII over-expressing cells were reported to have higher levels of phosphorylated Stat3 as compared to empty vector control cells.[22] Wildtype EGFR expressing cells were sensitive to cetuximab, a humanized anti-EGFR antibody, but cells expressing EGFRvIII were not affected by cetuximab treatment.[22] Furthermore, expression of EGFRvIII was sufficient to transform and enhance the motility of normal mouse fibroblasts.[23]

c-Met, a RTK, is over-expressed in HNSCC and involved in enhancing proliferation, motility and invasion. The hepatocyte growth factor (HGF) is the ligand for c-Met.[24] Binding of HGF activates c-Met resulting in phosphorylation of PI3K/Akt and mitogen activated protein kinase (MAPK) and activation of Stat3.[25, 26] High serum levels of HGF were reported to be associated with resistance to chemoradiation and poorer survival.[27] Activation of c-Met by HGF results in signaling leading to tumor growth, metastasis, and angiogenesis.[28] Primary HNSCC tumors were shown to have elevated levels of HGF and c-Met in comparison to adjacent normal epithelium.[29] In addition, HNSCC patients with low c-Met and HGF in the primary tumor have better overall prognosis.[29] HNSCC cells treated with an anti-HGF antibody had impaired cell invasion and migration.[29] Moreover, amplification or mutation of c-Met enhance migration and metastasis in HNSCC.[30]

Another RTK, TrkB, was reported to be expressed in more than 50% of HNSCC tumor along with its ligand, brain derived neurotrophic factor (BDNF).[31] Stimulation of TrkB by BDNF enhanced invasion and migration of HNSCC cells.[31] Targeted suppression of TrkB in OSC19 HNSCC cells inhibited invasion and migration.[31] Forced expression of TrkB altered the expression of EMT markers in Tu138 HNSCC cells; E-cadherin levels were reduced and Twist levels were elevated.[31] Additionally, tumor growth was retarded in TrkB-deficient OSC19 HNSCC cells in nude mice.[31]

III. Signal transducer and activator of transcription 3

Signal transducer and activator of transcription 3 (Stat3) belongs to a family of transcription factors involved in cytokine signaling. Stat3 is activated through sequential phosphorylation of tyrosine 705 and serine 727 in response to various external stimuli. Receptor tyrosine kinases, EGFR and c-Met, phosphorylate Stat3 upon ligand binding.[25, 26, 32, 33] The binding of interleukin-6 (IL-6) to the gp130 receptor triggers Stat3 phosphorylation by JAK2.[34] Moreover, Stat3 was demonstrated to be a target of the c-Src non-receptor tyrosine kinase.[15] Upon activation, Stat3 homodimerizes and translocates to the nucleus to bind to specific DNA response elements to regulate gene expression.[35]

Stat3 was reported to be elevated and constitutively activated in HNSCC.[33, 36] Ectopic expression of constitutive active Stat3 in UMSCC22B, a HNSCC cell line with low endogenous active Stat3 levels, enhanced proliferation and tumorigenicity compared to control transfected cells.[37] UMSCC22B cells over-expressed with constitutive active Stat3 were shown to have elevated levels of cyclin D1 and Bcl-X_L, two recognized Stat3-dependent genes.[37] These results demonstrate that constitutively active Stat3 has the capacity to promote HNSCC tumorigenesis in an EGFR-independent manner. In support,

targeted suppression of Stat3 with a Stat3 decoy, a 15-mer double-stranded oligonucleotide to mimic the Stat3 response element, inhibited Stat3-mediated transcription and cell proliferation in HNSCC cells, PCI-37a and 1483.[38] These results provide evidence that Stat3 modulates cell proliferation and survival in HNSCC.

Epstein-Barr virus (EBV)-associated HNSCC is highly metastatic and has elevated Stat3 activation.[39] In fact, Stat3 phosphorylation was detected in 70-75% of EBV-associated primary HNSCC tumors.[39-41] A recent study demonstrated that EBV-induced Stat3 activation is directly responsible for promoting an invasive phenotype in HNSCC.[40] EBV-infected HONE-1 cells were shown to have elevated phosphorylated Stat3 at tyrosine 705 and a dramatic 11-fold increase in cell invasion compared to parental HONE-1 cells.[40] In addition, genetic ablation of Stat3 was sufficient to inhibit invasion in EBV-infected HONE-1 cells.[40] In a follow-up study, CNE-2 and HK1-LMP cells, two HNSCC cell lines with high levels of Stat3 activation, treated with cucurbitacin I, a JAK/STAT inhibitor, have impaired clonogenic survival and cell invasion and heightened sensitivity to anoikis.[42]

IV. Rho GTPases

Rho GTPases constitute a sub-family of the ras-superfamily of GTP-binding proteins. The Rho GTPase family is further subdivided into six different groups with the following members: Rho (RhoA, RhoB, and RhoC), Rac (RhoG and Rac1-3), Cdc42 (cdc42Hs, G25K, TC10), Rnd (Rho6, Rho7, and RhoE), RhoD and TTF.[43] Each Rho GTPase member is presumed to play a specific role in controlling cytoskeletal reorganization, membrane ruffling, cell motility, cell invasion, cellular proliferation, cell trafficking, and certain aspects of p53-independent/Bcl2-dependent apoptosis.[43-47] Rho proteins are involved in actin stress fiber and focal adhesion contact formation.[48] Rac and Cdc42 are primarily involved in the formation of lamellipodia and filipodia, respectively.[48]

Rho GTPases acts as an on-off switch (whether it is bound to GTP or GDP, respectively), capable of activating a large number of downstream Rho effectors. The Rho effectors are divided into three classes according to sequence homology: class I (protein kinase N (PKN), rhotekin, and rhophillin), class II (represented by Rho-kinase/ROK/ROCK), and class III (represented by citron).[47, 49-51] Specific downstream effector binding domains in the Rho GTPase protein are responsible for the activation of the different classes of targets.[52] Through interactions with the different downstream effectors which lead to interactions with other signaling “hib” proteins such as LIM kinase or adducin, Rho GTPases can exert a variety of effects on the cell.[49, 53]

The literature on the role Rho GTPases in HNSCC is beginning to accumulate. RhoA, Rac2, and Cdc42 were found to be elevated in premalignant dysplastic and HNSCC cell lines in comparison to normal keratinocytes.[54] Furthermore, based on their immunohistochemistry analyses, RhoA was suggested to be a promising biomarker of malignancy and/or aggressiveness in HNSCC.[54] In support, hyaluronan (HA)-CD44-dependent cell migration is mediated thorough RhoA in HSC-3 HNSCC cells.[55] HA-mediated activation of RhoA enhanced phospholipase Cε activity resulting in phosphorylation of filamin through calmodulin-dependent kinase II (CaMKII).[55] Phosphorylated filamin has lowered capacity to crosslink F-actin leading to an increase in tumor cell migration.[55] Our group demonstrated that RhoC is over-expressed in Stage III and Stage IV regionally metastatic HNSCC compared to Stage I and II localized HNSCC.[56] Additionally, elevated RhoC was shown to be associated with advanced clinical stage and lymph node metastases in this cohort of previously untreated HNSCC patients.[56] Recent work from our laboratory showed that genetic ablation of RhoC in HNSCC cells, UMSCC1 and UMSCC11A, is sufficient to

dampen cell invasion and migration *in vitro*.[57] Moreover, the metastatic potential of RhoC-deficient UMSCC11A cells were severely compromised in NOD/SCID mice.[57]

Two independent studies demonstrate that Cdc42 activation is critical for galectin-1 (Gal-1)- and CCL19-chemokine receptor 7 (CCR7)-mediated cell invasion in HNSCC cells. Gal-1, a β-galactose binding lectin, was shown to be elevated in primary HNSCC tumors with positive lymph nodes compared to primary HNSCC tumors without nodal disease.[58] Over-expression of Gal-1 in OC-2, a minimally invasive HNSCC cell line with low Gal-1 levels, enhanced Cdc42 activation resulting in an increase in cell invasion *in vitro* and lung metastasis in nude mice.[59] CCL19, a ligand for CCR7, stimulation of HNSCC cells enhanced cell invasion and migration through Cdc42 activation. Cdc42 was shown to be localized at the leading edge of migrating tumor cells. In addition, siRNA-mediated knockdown of Cdc42 is sufficient to blunt CCL19-induced cell invasion and migration.

There is also evidence to support the importance of Rac1 in mediating metastasis in HNSCC. Rac1 was shown to be active in a majority of HNSCC cell lines while RhoA and Cdc42 activation was restricted to a selective number of HNSCC cell lines.[60] HNSCC cell lines with enhanced Rac1 activation were associated with a highly invasive and motile tumor cell phenotype.[60] Constitutive Rac1 activation was demonstrated to be a result of EGFR phosphorylation and activation of Vav2, a Rac1 guanine nucleotide exchange factor (GEF).[60] Thus, there is evidence that the EGFR-Vav2-Rac1 signaling axis is critical for driving a metastatic phenotype in HNSCC.[60] In addition, Rac1 was reported to be required for integrin-mediated cell invasion and migration in HNSCC. Epidermal growth factor receptor pathway substrate 8 (Eps8) facilitates cell migration by regulating F-actin and focal adhesion kinase (FAK) activity.[61, 62] Elevated Eps8 levels were shown to be associated with positive nodal disease in HNSCC.[63] Genetic ablation of Eps8 suppressed integrin-mediated cell migration.[63] Recapitulation of active Rac1 was sufficient to rescue the cell migration defect of Eps8-deficient HNSCC cells.[63] Lastly, Rac1 also was demonstrated to be critical for integrin-mediated cell invasion in HNSCC.[64]

V. Protein kinase Cε

Protein kinase C (PKC) is a family of serine/threonine kinases known to play critical roles in the signal transduction pathways involved in proliferation, differentiation, apoptosis, and migration.[65-67] Ten different PKC isoforms have been identified and are divided into three groups according to their structure and activation requirements. The classical isoforms, α, βI, βII, and γ, have intact C1 diacylglycerol/phorbol ester binding domain and C2 calcium binding domain and thus, require phospholipids and calcium for activation. The novel isoforms, δ, ε, ζ, and η, are calcium-independent and the atypical isoforms, θ, and ι/λ, can be activated in the absence of diacyglycerol and calcium.

In primary HNSCC tumors, PKCα, β, γ, ε, and ζ levels were shown to be elevated but only PKCε was found to be a prognostic biomarker, even better than the traditional gold standard of TNM staging.[68] This prospective study indicated that elevated PKCε is significantly associated with an increase in disease recurrence and a decrease in overall survival.[68] Our laboratory demonstrated that PKCε is elevated in HNSCC and promotes an invasive and motile tumor cell phenotype.[69] RNAi-mediated knockdown of PKCε in UMSCC11 and UMSCC36, two HNSCC cell lines with elevated endogenous PKCε levels, is sufficient to significantly impair cell invasion and migration.[69] Moreover, reconstitution of constitutive active RhoA or RhoC in PKCε-deficient HNSCC cells is sufficient to rescue the loss-of-function migration defect providing direct evidence that RhoA and RhoC is downstream of the PKCε signaling cascade.[69] In addition to regulation of Rho GTPases, PKCε was reported to directly phosphorylate and activate Akt and Stat3. PKCε phosphorylates Akt at serine 473

and Stat3 at serine 727 leading to their full activation/functional state.[70-72] There is emerging evidence that Akt phosphorylates RhoC to enhance RhoC activation.[73] ROK, a downstream Rho effector, phosphorylates Stat3 resulting in an increase in Stat3 nuclear translocation.[74] In addition, PKCε has been reported to be involved in HGF-c-Met signaling in HNSCC.[75, 76] Based on these observations, the PKCε signaling network comprises of several highly interconnected signaling nodes, Rho GTPases, Akt, Stat3, and c-Met, to modulate cell invasion, migration, and survival in HNSCC cells.[77]

VI. Nuclear factor-κB

NF-κB is a transcription factor which functions as a master regulator of genes involved in numerous cellular processes, including inflammation, immune response, cell proliferation, apoptosis and invasion. The process of inflammation is postulated to be a trigger for oncogenesis and NF-κB has been identified as the link to connect chronic inflammation to cancer development. HNSCC tumors and cell lines was reported to have constitutive NF-κB activation resulting in a global increase in pro-inflammatory and pro-angiogenic cytokines, such as interleukin-6 (IL-6) and interleukin-8 (IL-8).[78, 79] Increased nuclear localization of NF-κB is associated with poor prognosis in HNSCC patients.[80, 81] Moreover, NF-κB also has been reported to play a role in the development of resistance to chemotherapeutics in HNSCC.[82, 83] Several lines of evidence exist to indicate that NF-κB is involved in HNSCC metastasis. Nuclear NF-κB staining was detected in 52% of primary HNSCC tumors with positive nodes compared to only 23% of primary HNSCC tumors without positive nodes.[84] Pharmacological blockade of NF-κB blunted cell migration in highly metastatic Tb and TL HNSCC cell lines.[84] Moreover, lung and lymph node metastasis of TL cells in two animal models was severely suppressed with a selective NF-κB inhibitor, pyrrolidine dithiocarbamate.[84] Urokinase-type plasminogen activator (uPA), a validated NF-κB-regulated gene, is intimately involved in metastasis in part through modulation of extracellular matrix proteolysis and cytoskeleton rearrangement. Elevated uPA levels were associated with an invasive phenotype in HNSCC cell lines.[85] In direct support, increased uPA expression in primary HNSCC tumors was demonstrated to be predictive of positive lymph nodes.[86] Moreover, elevated uPA levels correlated with tumor relapse in HNSCC.[87]

There is evidence that NF-κB regulates Stat3 activation through control of IL-6. Activation of the gp130 receptor with IL-6 leads to JAK2-mediated phosphorylation of Stat3 at tyrosine 705 in an EGFR-independent manner.[34] HNSCC cells, HN13 and HN30, were shown to express high levels of IL-6 through NF-κB-dependent transcriptional activation.[88] Genetic inhibition of NF-κB reduced IL-6 levels resulting in a decreased in Stat3 phosphorylation and activation in HNSCC cells.[88] Moreover, immunohistochemistry analysis of primary HNSCC tumors showed a correlation between NF-κB, IL-6, and phosphorylated Stat3.[88]

VII. Summary

HNSCC patients with metastatic disease have limited treatment options and are often offered palliative care. A critical need exists to better understand the genetic alterations which facilitate cellular processes required for metastasis, including invasion, migration, and survival. Acquisition of a metastatic tumor cell phenotype is a complex process and may require the coordinated effort of numerous signal transduction pathways. There is accumulated literature to demonstrate that RTKs, Stat3, Rho GTPases, PKCε, and NF-κB play critical roles to promote metastasis in HNSCC. These five key signaling cascades are highly interconnected in HNSCC suggesting that crosstalk may be necessary to efficiently reprogram a tumor cell to acquire the potential to drive metastatic disease. A system biology approach is necessary to begin to understand the minimal genetic alterations required to promote a metastatic tumor cell phenotype in HNSCC. Detailed understanding of the global

metastasis signaling network, including temporal and intensity dynamics, is essential in order to identify critical integration points in the signaling cascade to optimize therapeutic efficacy and minimize adverse effects. This approach will lead to the development of novel anti-cancer therapeutics and hopefully improve the prognosis of HNSCC patients with metastatic disease.

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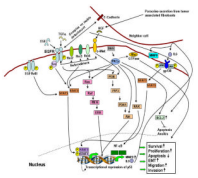

Figure 1.
Regulation of Metastasis in HNSCC.