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Signaling Pathways Supporting Tumor Invasion in Head and Neck Squamous Cell Carcinoma

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Abstract

Head and neck squamous cell carcinoma (HNSCC) is a highly invasive cancer. A number of signaling pathways like PI3K, Rho and TGFβ/SMAD drive the invasive nature of HNSCC. The PI3K pathway is the most altered pathway in HNSCC. Both upstream and downstream members of this pathway have been found to be mutated or overexpressed leading to an increase in cell invasion. The Rho pathway is also commonly activated; however, only overexpression or downregulation of Rho's upstream regulators are found in HNSCC. Finally, TGFβ/SMAD pathway activation leads to epithelial mesenchymal transition in HNSCC and subsequently invasion, though loss of TGFβ/SMAD signaling has also been shown to increase cell invasion.

Keywords: Invasion; HNSCC; PI3K; EGFR; Rho; SMAD; TGFβ

Abbreviations

HNSCC: Head and Neck Squamous Cell Carcinoma; PI3K: Phosphoinositide 3-Kinase; Rho: Ras Homologue; RTK: Receptor Tyrosine Kinase; EGFR: Epidermal Growth Factor Receptor; FGFR: Fibroblast Growth Factor Receptor; GTPase: small Guanosine Triphosphatase; HRAS: Harvey Rat Sarcoma Viral Oncogene Homolog; PIP2: Phosphatidylinositol 4,5-Bisphosphate; PIP3: Phosphatidylinositol (3,4,5)-Trisphosphate; PTEN: Phosphatase And Tensin Homolog; PDK-1: Phosphoinositide-Dependent Kinase-1; AKT: Protein Kinase B; TSC1: Tuberous Sclerosis 1; TSC2: Tuberous Sclerosis 2; mTORC1: Mechanistic Target Of Rapamycin Complex 1; mTORC2: Mechanistic Target Of Rapamycin Complex 2; EIF4E: Eukaryotic Translation Initiation Factor 4e; EGF: Epidermal Growth Factor; SphK1: Sphingosine Kinase-1; TGFα: Transforming Growth Factor A; HER2: Human Epidermal Growth Factor Receptor 2; c-MET: Hepatocyte Growth Factor Receptor; MMP9: matrix metalloprotease 9; SGK-1: Serum/Glucocorticoid Regulated Kinase 1; GSK3β: Glycogen Synthase Kinase-3 B; EMT: Epithelial-Mesenchymal Transition; ADAM12: Disintegrin And Metalloproteinase Domain-Containing Protein 12; EMPPRIN: Extracellular Matrix Metalloproteinase Inducer; COX2: Prostaglandin-Endoperoxide Synthase 2; PKC: Protein Kinase C Epsilon; p120ctn: p120-Catenin; S100A4: S100 Calcium Binding Protein A4; TGFβ: Transforming Growth Factor B; ROCK1: Rho Associated Protein Kinase 1; ROCK2: Rho-Associated Protein Kinase 2; PI4P5K: Phosphatidylinositol-4-Phosphate 5-Kinase; DIAPH1: Protein Diaphanous Homolog 1; MLCK: Myosin Light Chain Kinase; Rac1: Ras-Related C3 Botulinum Toxin Substrate 1; PAK1: p21 Activated Kinase; Arp2/3: Actin-Related Proteins 2 and 3; FAK: Focal Adhesion Kinase 1; src: V-Src Avian Sarcoma (Schmidt-Ruppin A-2) Viral Oncogene Homolog; cdc42: Cell Division Control Protein 42 Homolog; CCR7: Chemokine Receptor Type 7; VEGF: Vascular Endothelial Growth Factor; LEF1: Lymphoid-Enhancer Binding Factor 1; TAK1: TGFβ-Activated Kinase 1; IL-8: Interleukin-8; IL-1: Interleukin-1; TNFα: Tumor Necrosis Factor α.

Introduction

Head and neck squamous cell carcinoma (HNSCC) is a term covering a group of cancers arising from the squamous epithelia in the head and neck region. The public health burden of HNSCC is profound, with ~300,000 people living with the disease in the United States. Approximately 40% of patients die within 5 years of diagnosis [1]. The treatment of HNSCC frequently entails large, disfiguring surgical excisions. Thus, of those who survive the disease, a large fraction has substantial functional and cosmetic morbidity. Precise characterization of the pathways involved in HNSCC invasion is very useful, as this understanding may allow for earlier diagnosis and better treatment.

Multiple risk factors have been found to contribute to the development of HNSCC. An estimated 73% of all HNSCCs are due to the combined effects of tobacco smoking and alcohol consumption [2]. The most prominent risk factor is tobacco smoking, which multiplies the risk of developing HNSCC by 6 to 13 times [3-5]. In addition to tobacco and alcohol, many other risk factors like viral infections (Epstein Barr Virus and Human Papillomavirus), radiation, chemical exposures due to occupational hazards and diet can contribute to the development of this deadly disease [6-10]. Some of these risk factors directly affect the signaling pathways that are involved in HNSCC invasion.

The majority of HNSCCs appear to have modifications in the same signaling pathways despite the variety of risk factors and anatomical locations of origin. The three pathways that appear to be most consistently modified are the Phosphoinositide 3-kinase (PI3K), Ras homologue (Rho) and TGFβ/SMAD pathways [11-13]. These pathways have been found to be responsible for neoplastic transformation. They have also been implicated in cancer invasion, a prerequisite to the development of metastatic disease [14,15]. Much work has focused on changes to the PI3K, Rho and TGFβ/SMAD pathways in HNSCC, but only a portion of it has focused on the invasive capacity of HNSCC.

PI3K Pathway

The PI3K pathway is the most commonly activated pathway in HNSCC [12]. PI3K signaling occurs downstream of the cell surface receptor tyrosine kinases (RTKs), such as epidermal growth factor receptor (EGFR) or fibroblast growth factor receptor (FGFR) (Figure 1). Small Guanosine Triphosphatases (GTPases) like Harvey rat sarcoma viral oncogene homolog (HRAS) can also activate the PI3K pathway. PI3K is a protein kinase that phosphorylates phosphatidylinositol 4,5-bisphosphate (PIP2) into its active form, phosphatidylinositol (3,4,5) trisphosphate (PIP3). The opposite activity to PI3K is performed by phosphatase and tensin homolog (PTEN), which works by dephosphorylating PIP3 to deactivate it. Conversion of PIP2 to PIP3 leads to recruitment of phosphoinositide-dependent kinase-1 (PDK-1) and protein kinase B (AKT) to the plasma membrane. PDK-1 phosphorylates threonine 308 of AKT resulting in AKT activation. Activated AKT phosphorylates tuberous sclerosis 1 (TSC1) and tuberous sclerosis 2 (TSC2) resulting in the activation of the mechanistic target of rapamycin complex 1 (mTORC1) and mechanistic target of rapamycin complex 2 (mTORC2) that signal further downstream (Figure 1). mTORC1 signaling through eukaryotic translation initiation factor 4e (EIF4E) results in increased protein synthesis while mTORC1 signaling through S6K has been associated with increased mRNA synthesis, cap dependent translation and elongation, and translation of ribosomal proteins. mTORC2 signaling has been less studied than mTORC1 and so large gaps of knowledge still exist regarding its function. However, mTORC2 is thought to affect cell survival, proliferation and cytoskeletal organization [16]. Interestingly, PI3K pathway members are activated by HNSCC's primary risk factor, tobacco smoking. Nicotine contained in tobacco smoke binds nicotinic acetylcholine receptors leading to activation of AKT and mTORC1 [17].

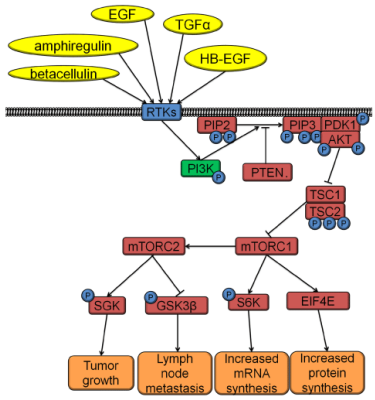

Figure 1: PI3K signaling pathway.

PI3K pathway activation leads to neoplastic transformation and tumor formation in many tissues. Thus far, research regarding tumor initiation in HNSCC is still limited. Increased PI3K pathway activity immortalizes oral keratinocytes by AKT-dependent phosphorylation and activation of hTERT [18]. A carcinogen-induced oral cancer model implicates the PI3K pathway in HNSCC tumor initiation. In this animal model, RTKs that signal through the PI3K pathway are frequently mutated and overexpressed in the developing tumors [19]. In tissues such as skin, mammary and lymphoid (T-cells), PTEN deletion triggers tumor development [20-22]. Moreover, AKT phosphorylation is known to be one of the first steps in chemical-induced carcinogenesis of epidermal keratinocytes [23]. The activated PI3K pathway promotes tumor initiation by increasing cell proliferation and inhibiting apoptosis. AKT phosphorylates CDKN1A (p21), which is then exported from the nucleus where it is unable to inhibit Cyclin/CDK complexes [24]. AKT also decreases the transcription of a cell proliferation inhibitor, CDKN1B (p27) [25]. Additionally, Cyclin D1 is up-regulated upon activation of the PI3K pathway [26]. Finally, activated AKT can phosphorylate BAD resulting in an inhibition of apoptosis [27]. Interestingly, data from cutaneous squamous cell carcinoma, indicates that PI3K signaling can phosphorylate and activate FOXO3 to regulate the expression of proteins involved in cell cycle and death such as ΔNp63, β-catenin, lymphoid-enhancer binding factor 1 (LEF1), C-MYC, and Cyclin D1 [28,29]. Breast cancer has a similar spectrum of PI3K pathway mutations as HNSCC. Mammary cells expressing mutant PIK3CA show increased growth and anchorage-independent survival due to increased NFκB activity [30,31]. Many of these pathway alterations leading to transformation still need to be investigated in HNSCC.

PI3K pathway activation plays a prominent role not only in HNSCC initiation, but also in HNSCC invasion. A number of RTKs and activation mechanisms lead to PI3K pathway activity and increased invasion in HNSCC. HNSCC tumors often secrete ligands, which lead to an autocrine activation of the PI3K pathway. Ninety one percent of HNSCC tumors have increased levels of transforming growth factor α (TGFα), an EGFR ligand [32,33]. In addition, treatment of HNSCC cell lines with EGFR ligands (e.g., epidermal growth factor (EGF), betacellulin, TGFα, heparin binding EGF and amphiregulin) increased cell invasion [34,35].

An additional mechanism of PI3K pathway activation is RTK overexpression. An overexpression of RTKs results in spontaneous receptor dimerization events. These consequently lead to ligand-independent receptor activation. Overexpression of RTKs like FGFR1, FGFR2, and FGFR3 on the HNSCC cell surface correlates with increased invasion and metastasis [36-38]. RTKs such as human epidermal growth factor receptor 2 (HER2) and hepatocyte growth factor receptor (c-MET), when overexpressed, increased cell invasion in vitro [39-41]. Besides RTK overexpression, PI3K pathway activation can also occur due to an RTK mutation. EGFRvIII, a constitutively active EGFR mutant, increased motility and cell invasion [42]. Finally, the PI3K signaling pathway can be activated due to the overexpression of sphingosine kinase 1 (SphK1). SphK1 transactivates EGFR and increases invasion [43].

PI3K pathway activation can occur due to activating mutations or overexpression of PI3K. The PI3K heterodimer is composed of an 85 kDa regulatory and a 110 kDa catalytic subunit. The PIK3CA gene codes for the 110 kDa subunit. This gene is overexpressed and mutated in 56% and 21% of HNSCC [12]. PIK3CA overexpression results in increased activation of the PI3K pathway and correlates with increased lymph node metastases in HNSCC [44]. Seventy three percent of all PIK3CA mutations are localized to three hotspots - residues 542, 545, and 1047 and cause constitutive activation of PI3K [12]. Mutations E542K and E545K are in the helical domain, while the H1047R mutation is in the kinase domain of the 110 kDa catalytic subunit. The gain-of-function helical domain mutations lead to PI3K activation by binding RAS and are not affected by the regulatory 85 kDa subunit. The mutations in the kinase domain activate PI3K independently of RAS via interaction with the regulatory 85 kDa subunit [45]. E542K, E545K, and H1047R mutants increase the invasive phenotype of

HNSCC cell lines [46]. However, E545K and H1047R induced different rates of invasion in a breast cancer model; therefore, additional work is needed to characterize these mutants [47].

The PI3K pathway's involvement in invasive properties of HNSCC comes from the pathway's effects on proteins involved in basement membrane breakdown and actin mobilization. PI3K pathway activation can increase the expression of MMP 1, 2, 3, 9, 12 and ADAM12 by increasing the expression of prostaglandin-endoperoxide synthase 2 (COX2) and extracellular matrix metalloproteinase inducer (EMPPRIN) [39,41,48,49]. MMP9 is also induced due to mTORC1 activity through EIF4E [17,50]. MMP2 and MMP9 degrade collagen IV, the main component of the basement membrane, facilitating cell invasion [51]. Interestingly, ADAM12 cleaves stromal proteins akin to metalloproteases, but can also increase HER2 expression, further activating the PI3K pathway [39]. In addition, the activity of SGK-1 and glycogen synthase kinase-3β (GSK3β), proteins downstream of mTORC1, led to invasion or EMT in other cell types [52,53]. Further studies are required to evaluate the role of SGK-1 and GSK3β in HNSCC invasion.

PI3K pathway activity has been shown to result in activation or increased expression of proteins regulating cytoskeleton rearrangement like RhoC, Vav2, and fibronectin [48,54]. Increased activity of RhoC, Vav2 and fibronectin correlates with increased cell invasion [35,48,55]. Activated RhoC increased invasion through E-cadherin downregulation in HNSCC [55]. Vav2 functions are still largely unknown. Vav2 interacts with both PI3K and EGFR to become activated, and acts as a guanine nucleotide exchange factor to activate GTPases. Some of the Vav2 regulated GTPases belong to the Rho family [56,57]. Finally, work in HONE1 cells, an HNSCC cell line, indicates that PI3K signaling enhanced fibronectin expression which activated the cell division control protein 42 homolog (cdc42) and Rac1, increasing cell invasion [48].

Rho Pathway

The Rho family of GTPases consists of signaling proteins that have been shown to regulate actin cytoskeleton rearrangement [58]. There are many members belonging to this protein family (e.g., RhoA, RhoC, ras-related c3 botulinum toxin substrate 1 (Rac1), cdc42). RhoA and RhoC are homologous proteins with differing affinity towards their effector proteins. The effects of RhoA and RhoC on invasion and migration differ in the cancer setting. RhoC activation always leads to increased migration and invasion, while RhoA activation appears to either increase or decrease invasion depending on the experimental system [55,59,60].

RhoA pathway activation occurs as a result of a guanosine diphosphate being replaced by a guanosine triphosphate in the RhoA by a guanine nucleotide exchange factor. The signal propagates through its effectors Rho associated protein kinase 1 (ROCK1), Rho-associated protein kinase 2 (ROCK2), phosphatidylinositol-4-phosphate 5-kinase (PI4P5K), and protein diaphanous homolog 1 (DIAPH1) (Figure 2). ROCK phosphorylates myosin light chain kinase (MLCK) and inhibits myosin phosphatase that de-phosphorylates MLCK. MLCK is responsible for cytoskeletal rearrangement. ROCK also activates adducin which binds F-actin filaments, leading to an increase in cell motility. LIM kinase, another target of ROCK, phosphorylates cofilin leading to actin filament cleavage which can contribute to increased cell motility. RhoA signaling via PI4P5K and DIAPH1 increases actin polymerization and cell motility (Figure 2) [61].

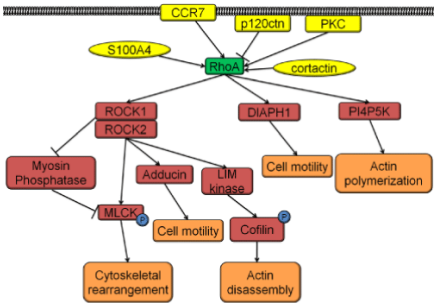

Figure 2: Rho signaling pathway.

There are multiple regulators of RhoA such as chemokine receptor type 7 (CCR7), cortactin, S100 calcium binding protein A4 (S100A4), protein kinase C epsilon (PKC), and p120ctn. Expression of CCR7, cortactin, and S100A4 is increased in HNSCC. Direct RhoA activation by CCR7 or cortactin, indirect RhoA activation by S100A4 via rhotekin, results in increased cell invasion [62-66]. PKC, also overexpressed in HNSCC, can activate RhoC in addition to RhoA. Even when PKC is inhibited, either RhoA or RhoC activity alone is enough to rescue the increase in motility [67]. Another very likely candidate controlling RhoA activity is p120ctn. This protein is frequently downregulated or lost in HNSCC [68]. In addition, p120ctn downregulation or loss in HNSCC has been correlated with poor prognosis [68]. p120ctn normally suppresses RhoA activity, and upon p120ctn loss, RhoA activity increases [69]. The effects of p120ctn are even more significant considering that tobacco smoking and alcohol consumption lead to a decrease in p120ctn expression [70-72]. Further studies are needed to explore the role of p120ctn in HNSCC since p120ctn deregulation can either decrease or increase the invasive capabilities of cells in vitro depending on the cell type [73,74].

Multiple factors lying downstream of RhoA have been shown to be activated in HNSCC and their activation has been linked to the process of invasion. p21 activated kinase (PAK1) is activated in HNSCC. PAK1 phosphorylates actin-related proteins 2 and 3 (Arp2/3) leading to actin mobilization [75]. FAK is overexpressed in HNSCC, though its expression has been shown not to correlate with increased gene copy number found in tumors [76]. RhoA signaling activates FAK, which colocalizes at the focal adhesions and promotes invasion by increasing MMP2 production in HNSCC cell lines [77]. Avian sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog (src) and fascin, proteins directly controlling actin localization and invadopodia formation, are also activated in HNSCC downstream of Rho. Src and fascin activity was correlated with HNSCC invasion and lymphatic metastasis, respectively [78,79].

TGFβ/SMAD Pathway

TGFβ/SMAD signaling can either suppress or support cancer progression [80, 81]. However, the exact role it plays in HNSCC is yet to be determined. The pathway is activated by transforming growth factor β (TGFβ) binding its cell surface receptor and phosphorylating either SMAD2 or SMAD3, which form a heterotrimeric complex with SMAD4 (Figure 3). The complex translocates to the nucleus where it leads to the transcription of target genes. These genes result in

increased invasion (e.g., MMP2, MMP9, SNAIL) or growth suppression (e.g., p21, p12CDK2-AP1, p15-INK4B) [82-87]. SMAD6 and SMAD7 are inhibitory SMADs that prevent SMAD2/3 from getting phosphorylated (Figure 3).

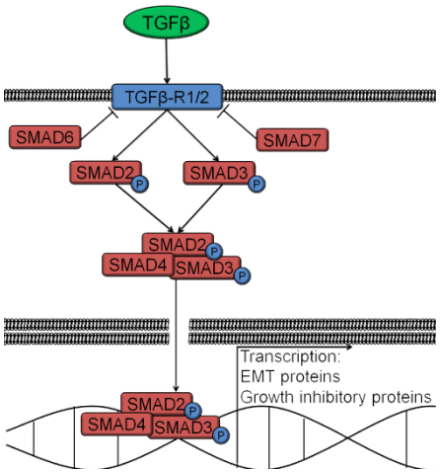

Figure 3: TGFβ/SMAD signaling pathway

The effects of TGFβ/SMAD signaling in HNSCC are still a matter of debate. TGFβ/SMAD pathway activation results in EMT, a process commonly associated with invasion and metastasis. TGFβ expression is increased in tumor samples from HNSCC patients [88]. In addition, work in HNSCC cell lines revealed that activation of the TGFβ/SMAD pathway by TGFβ drives increased cell motility. TGFβ treatment of HNSCC cell lines also results in increased expression of EMT proteins such as SLUG, leading to increased invasion [87,89]. Additionally, TGFβ treatment increases MMPs and extracellular matrix protein expression in an HNSCC cell line, SCC9 [90]. TGFβ/SMAD signaling activation in HNSCC increased cellular motility, expression of EMT proteins such as SNAIL and increased MMPs, leading to increased invasion [91-93]. Moreover, TGFβ-activated inhibitory proteins such as p21, p12CDK2-AP1 and p15-INK4B are often mutated in HNSCC, which allows increased cell invasion due to TGFβ/SMAD signaling without undergoing cell cycle arrest [82-86].

In addition to the autocrine effects TGFβ has on tumors, TGFβ also supports tumor invasion by its effects on the tumor microenvironment. Immune cells, such as macrophages, are recruited to the tumor site by TGFβ secreted by tumor cells. In the tumor stroma, the macrophages undergo activation and secrete Vascular Endothelial Growth Factor (VEGF) and Interleukin-8 (IL-8) leading to neo-vascularization. Macrophages also secrete Tumor Necrosis Factor α (TNFα) and Interleukin-1 (IL-1) which stimulate the tumor cells themselves to also secrete VEGF and IL-8 further potentiating neo-vascularization [94]. Increased levels of VEGF in HNSCC have been correlated with increased metastasis [95]. In addition, stromal fibroblasts also promote HNSCC invasion. Tumor-secreted TGFβ induces fibroblasts to secrete Hepatocyte Growth Factor, which can bind c-MET in tumor cells and increase their invasive capabilities [96]. Moreover, HNSCC-produced reactive oxygen species induce senescence in the stromal fibroblasts. These senescent fibroblasts secrete an increased amount of TGFβ thus promoting keratinocyte invasion [97].

While the activation of the TGFβ/SMAD signaling pathway can increase invasion in HNSCC, inhibition of TGFβ/SMAD signaling in HNSCC has also been shown to increase cell invasion. Multiple reports indicate that decreased levels of TGFβ1 and TGFβ2 receptors in HNSCC are the result of mutations or promoter hypermethylation [98-101]. TGFβ/SMAD signaling is disrupted in close to 50% of human HNSCCs. Mutations in TGFβ/SMAD pathway have been associated with a poor prognosis in HNSCC [102]. TGFβ1 receptor loss with concomitant loss of PTEN resulted in invasive HNSCC in mice [13]. Also, when SMAD4 is deleted in mice it leads to HNSCC development with evidence of cellular invasion [103]. In addition, SMAD2 and SMAD4 are frequently mutated in HNSCC cell lines due to nonsense and missense mutations [104]. Deletion of SMAD4, which leads to inhibition of TGFβ/SMAD signaling, increased cell invasion in the HNSCC cell line FaDu-Hyg-R [105]. It is still unclear what mechanisms are responsible for increased invasion in HNSCC due to TGFβ/SMAD signaling pathway inhibition. Work in esophageal keratinocytes, a cell type closely related to squamous epithelium of the head and neck region, implicates the secretion of proteases and change in integrin expression as the way in which TGFβ/SMAD signaling pathway inhibition leads to invasion [106]. Alternatively, SMAD4 loss in colorectal carcinoma leads to invasion by activating the Rho pathway [107]. Further investigation is necessary to identify the exact mechanism used to drive cell invasion in HNSCC due to TGFβ/SMAD signaling pathway inhibition.

Pathway Crosstalk

As with most signaling pathways, the PI3K, TGFβ and Rho pathways have common protein targets and therefore crosstalk is common among these three pathways in HNSCC (Figure 4). PI3K-AKT and Rho-ROCK signaling both phosphorylate STAT3 and increase HNSCC invasion [42,108,109]. All three pathways: Rho, PI3K and TGFβ lead to NFκB activation. IκK can be activated by ROCK (a Rho target), TGFβ-activated kinase 1 (TAK1), and AKT (a PI3K target).

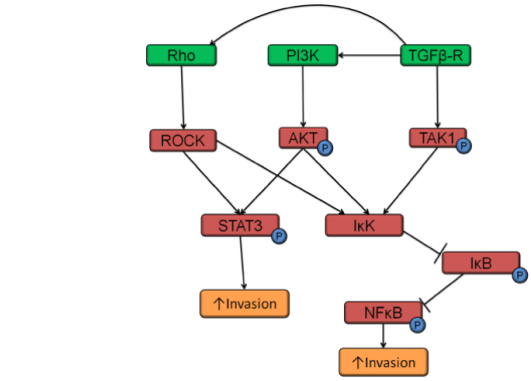

Figure 4: Pathway crosstalk.

In turn, IκK phosphorylates IκB (which undergoes proteosomal degradation) and NFκB resulting in its activation and translocation to the nucleus [110-113]. Activated NFKB in HNSCC correlates with increased invasion [114]. In addition, TGFβ/SMAD signaling can also activate Rho and PI3K signaling pathways resulting in EMT (Figure 4) [115,116]. In TGFβ1 receptor knockout mice, PI3K pathway activation was critical for tumor development [117]. Loss of TGFβ signaling led

to the development of invasive HNSCC only when coupled with increased PI3K pathway signaling [13].

Summary

In conclusion, the PI3K pathway becomes activated in HNSCC, leading to invasion due to multiple members of the pathway being mutated or overexpressed. Even though the PI3K pathway has been studied intensely in the last few decades, it is still unclear which members of the pathway are essential to the process of invasion. The Rho pathway, which directly deals with cytoskeletal rearrangement, is also commonly activated in HNSCC. Upon activation, this pathway leads to increased invasion in HNSCC. Moreover, HNSCC risk factors like tobacco smoking and alcohol consumption activate Rho signaling. Additionally, it is not clear whether activated or repressed TGFβ/SMAD signaling leads to increased invasion in HNSCC. It is possible that there are two subtypes of HNSCC, one with increased and one with decreased TGFβ/SMAD signaling. Further studies are required to validate the role of TGFβ/SMAD signaling in HNSCC. Finally, the complexity is also increased by the cross-activation between the PI3K, Rho and TGFβ/SMAD signaling pathways. It is possible that each of these pathways further increases HNSCC invasion through their activation of each other.

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