Research Perspective

A highway to carcinogenesis: the role of IQGAP1, a signaling scaffolding protein, in head and neck cancer development

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ABSTRACT

Head and neck squamous cell carcinoma (HNSCC) is the sixth most frequent cancer worldwide. One of the most critical signaling pathways in HNSCC is the Epidermal Growth Factor Receptor/ Phosphatidylinositol 3-Kinase (EGFR/PI3K) pathway. IQ motif-containing GTPase- activating protein 1 (IQGAP1), a protein upregulated in multiple types of cancer, acts as a scaffold for this pathway and others implicated in cancer. IQGAP1 is overexpressed in HNSCCs, and its overexpression correlates with poorer prognosis in HNSCC patients, indicating that IQGAP1 might be important in HNSCC development. Here, we summarized our recent demonstrating a role of IQGAP1 in promoting HNSCC, at least in part, by scaffolding the EGFR/PI3K signaling pathway.

INTRODUCTION

HNSCCs, which arise in the mouth and throat region, are the sixth most frequent cancer worldwide, with approximately 53,000 new cases and 11,000 associated deaths in the United States in 2019 [1]. The 5-year survival rate for head and neck cancer patients is about 60% [1]. Activation of the EGFR/PI3K pathway is observed in up to 74% of HNSCCs [2, 3]. *PIK3CA*, which encodes for the catalytic subunit of PI3K, is amplified in > 40% of HNSCCs, and contains gain-of function mutations in about 20% of HNSCCs [2, 4, 5]. These *PIK3CA* mutations correlate with advanced-stage HNSCCs, promoting HNSCC cell growth, tumor progression, invasion and metastasis [6–10]. Unfortunately, the efficacy of targeted therapies involving small molecule inhibitors of the EGFR/PI3K pathway has been limited due to the toxicity and possible drug resistance, raising the urgency of searching for other drug targets in the EGFR/PI3K signaling for more effective treatment of HNSCC patients [11, 12].

IQ motif-containing GTPase-activating protein 1, (IQGAP1), is a scaffolding protein that speeds up the efficiency of intracellular signaling by assembling multiple factors that mediate these signaling pathways. IQGAP1 affects multiple cellular activities such as cytoskeletal dynamics, cell-cell adhesion, cell proliferation, cell motility and invasion [13–16]. IQGAP1 is overexpressed in many human cancers, including breast, lung, colorectal cancers and HNSCCs [13, 16–18]. In HNSCCs, high levels of IQGAP1 expression correlates with poorer prognosis for the patients [18, 19]. IQGAP1 binds directly to EGFR and facilitates its ligand-dependent activation [20]. It also acts as a scaffold for the PI3K signaling pathway that is downstream of EGFR by assembling all of the kinases mediating production of phosphatidylinositol (3, 4, 5)-trisphophate (PIP3) upon EGFR receptor activation, which in turn results in increased phosphorylation of AKT (the activated form of AKT), a downstream effector of EGFR/PI3K signaling [21]. In a previous study, IQ3 peptide, a cell permeable peptide containing the PI3K binding motif on IQGAP1, was designed to specifically block the interaction between IQGAP1 and PI3K, and therefore inhibits IQGAP1-mediated PI3K signaling [21]. Treatment of HNSCC cell lines with IQ3 peptide, suppressed PI3K signaling, and inhibited cell survival, proliferation, migration and invasion, indicating that IQGAP1-mediated PI3K signaling is critical for human HNSCC cells [19, 22]. Reducing levels of IQGAP1 also resulted in decreased levels of phosphorylated-AKT (pAKT) in human HNSCC cell lines [19]. Likewise

we found that mice germ-line deficient for IQGAP1 (*Iqgap1*$^{-/-}$, [23]) showed reduced levels of both pAKT and phosphorylated-S6 (pS6, downstream of AKT), compared to wild type (*Iqgap1*$^{+/+}$) mice, when stimulated with EGF [19], demonstrating that IQGAP1 contributes to the efficiency of the EGFR/PI3K signaling pathway *in vivo*.

Considering the importance of PI3K signaling in HNSCCs, we explored whether IQGAP1 plays a role in head and neck carcinogenesis using a well-validated mouse model that drives HNSCC using a synthetic oral carcinogen, 4-nitroquinoline 1-oxide (4NQO, [24]). After 4NQO treatment, *Iqgap1*$^{-/-}$ mice developed significantly lower cancer incidences, lesser disease severity, and fewer cancer foci per mouse, when compared to the *Iqgap1*$^{+/+}$ mice [19]. Tumors arising in *Iqgap1*$^{-/-}$ mice showed significantly lower levels of PI3K signaling than those in *Iqgap1*$^{+/+}$ mice, indicating that IQGAP1 contributes to HNSCC, at least in part, through PI3K signaling [19]. In human HNSCCs samples, levels of PI3K signaling correlates positively with levels of IQGAP1, further supporting the link between IQGAP1 and PI3K signaling in HNSCCs [19].

Other than increasing PI3K signaling, there are other possible mechanisms by which IQGAP1 may drive HNSCCs. In skin, IQGAP1 promotes tumorigenesis by scaffolding the Ras-MAPK signaling pathway [25]. However, in our study, we observed a reduction of the Ras-MAPK signaling in tumors compared to adjacent normal areas, regardless of IQGAP1 status [19] indicating that activation of this pathway might not be critical in HNSCC at least in this mouse model. IQGAP1 also mediates Wnt signaling by binding to multiple components along the Wnt pathway that mediate Wnt-dependent transcription [13, 26]. In a subset of HNSCC, increased β-catenin, a downstream effector and transcription factor for Wnt signaling, was observed in cancer cells compared to normal tissue [27]. This leaves open the possibility that IQGAP1 could also be contributing to HNSCC by mediating Wnt signaling pathway.

IQGAP1 binds to both wild type and mutated PI3K [21]. Both breast cancer and HNSCC cell lines carrying *PIK3CA* mutations or wild-type *PIK3CA* respond to IQ3 peptide treatment [19, 21]. This makes the IQGAP1-PI3K interaction a potential drug target for HNSCC patients with either wild type or mutant PI3K. *PIK3CA* mutation also correlates with shorter time to disease recurrence in a subset of HNSCC [28]. These HNSCC patients could potentially benefit from drugs targeting the IQGAP1-PI3K interaction, such as the IQ3 peptide or a peptidomimetic small molecule. More studies are needed to understand the underlying mechanism(s) by how IQGAP1 contributes to HNSCC, which will shed more lights on hunting for new HNSCC therapeutic targets.

CONFLICTS OF INTEREST

The authors declare no potential conflicts of interest.

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