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Frequent Loss of Inositol Polyphosphate-5-Phosphatase in Oropharyngeal Squamous Cell Carcinoma

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There is an incomplete understanding in the pathogenesis of oropharyngeal squamous cell carcinoma (OPSCC) and cancer broadly. It is essential to discover new pathways of normal cell-cycle regulation and oncogenesis. We identified that the loss of inositol polyphosphate-5-phosphatase (INPP5A) may play a role in the development and progression of cutaneous squamous cell carcinoma (SCC).¹ Loss of INPP5A has been previously linked to cancer development and progression.² Inositol signaling pathways are involved in intracellular calcium release, membrane trafficking, chemotaxis, ion channel activity, and many other nuclear functions.³ Inositol signaling is highly conserved throughout the animal kingdom and plays a key role in gene regulation.

We hypothesized that, like cutaneous SCC, INPP5A expression will be decreased in OPSCC and that progressive reduction of INPP5A will occur with the transition from primary to metastatic disease. To test this hypothesis, we assessed INPP5A protein levels, using immunohistochemistry (IHC), in patients with primary OPSCC with matched lymph node metastasis.

Mayo Clinic Institutional Review Board approved this study. A prospective database of head and neck cancer patients treated from 1994–2014 with OPSCC at Mayo Clinic Arizona and Rochester was reviewed. A total of 40 cases were identified with both archived primary OPSCC tissue and matched metastatic lymph node tissue. One case had inadequate lymph node tissue. Stained slides were evaluated with the normal mucosa acting as the internal control. A scoring system was used to assess the intensity of staining (0–3) with a score of 0 representing no staining and score of 3 as intense staining.¹

INPP5A expression by IHC demonstrated diffuse cytoplasmic staining in normal tissue with a diminished staining within the tumor (Fig. 1). A comparison of INPP5A staining intensity

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between primary OPSCC samples and the internal controls showed a relative reduction of INPP5A staining in 22/40 (55%) cases (Table 1). To assess the role of INPP5A loss in the process of disease progression, we measured the IHC staining of 39 primary OPSCC with matched lymph node metastasis. IHC analysis of these paired tissues detected a further reduction of INPP5A staining in 13/39 (33.3%) cases, no relative change in 20/39 (51%) cases, and an increase in 6/39 (15%) cases respectively. There were no cases in which the primary or the metastatic disease had higher staining intensity than the matched normal mucosa.

We have identified decreased expression of INPP5A in primary and metastatic OPSCC. This data indicates an association of INPP5A loss with OPSCC development and disease progression.

Our findings strengthen previously reported observations that implicate INPP5A's role in human cancers. The loss of the chromosomal region 10q26, which encodes INPP5A, is associated with brain tumors and decreased INPP5A activity is associated with human leukemias.^{4–8} Our prior study in cutaneous SCC found that the INPP5A gene was lost in 24% of tumors and had decreased protein expression in 72% of primary tumors.¹ Additionally, primary cutaneous SCC with metastasis showed a loss in 92% of cases.¹

The precise mechanism(s) of INPP5A loss in SCC is unknown and a better understanding between INPP5A and uncontrolled cellular proliferation in cutaneous and mucosal SCC may provide novel insights into the pathogenesis of SCC and result in novel therapies. For example, murine models of cutaneous carcinogenesis found that bypassing the loss of INPP5A with IP6 reduced tumor formation at the initiation phase of carcinogenesis.⁹ In vitro studies of other cancers, such as breast, have shown the efficacy of IP6 as monotherapy and in combination with chemotherapy in resistant cell lines.¹⁰

In conclusion, INPP5A expression is commonly decreased in OPSCC, correlates with disease progression, and represents a potential prognostic and therapeutic target.

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Figure 1.
Inositol polyphosphate-5-phosphatase (INPP5A) Expression in Oropharyngeal Squamous Cell Carcinomas (OPSCC) – The dotted black line delineates the decreased staining in the invasive tumor (left) compared to the normal mucosa (right).

Table 1

Comparison of INPP5A protein levels in normal mucosa, primary oropharyngeal squamous cell carcinoma (OPSCC), and metastatic SCC

INPP5A staining intensity	Frequency
Primary OPSCC compared with matched normal mucosa	
Normal mucosa > primary OPSCC	22/40 (55%)
Normal mucosa = primary OPSCC	18/40 (45%)
Normal mucosa < primary OPSCC	0/40 (0%)
Metastatic SCC compared with matched normal mucosa	
Normal mucosa > metastatic SCC	23/39 (59%)
Normal mucosa = metastatic SCC	16/39 (41%)
Normal mucosa < metastatic SCC	0/39 (0%)
Primary OPSCC compared with matched metastatic SCC	
Primary OPSCC > Metastatic SCC	13/39 (33%)
Primary OPSCC = Metastatic SCC	20/39 (51%)
Primary OPSCC < Metastatic SCC	6/39 (15%)