## PROGNOSTIC SIGNIFICANCE OF NUCLEAR pSTAT3 IN ORAL CANCER

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**Abstract:** Background. Aberrant nuclear accumulation of proteins influences tumor development and may predict biologic aggressiveness and disease prognosis. This study determined the prognostic significance of pSTAT3 (phosphorylayed signal transducer and activator of transcription 3) in oral squamous cell carcinomas (OSCCs).

Methods and Results. Using immunohistochemistry, a significant increase in nuclear accumulation of pSTAT3 was observed in 49 of 90 leukoplakias (54.4%) and 63/94 OSCCs (67%) ( $p_{trend} < .001$ ). Increased pSTAT3 was associated with tumor stage (p = .01), nodal metastasis (p = .0018), and tobacco consumption (p = .004). Kaplan–Meier analysis demonstrated that OSCC with increased nuclear pSTAT3 showed significantly reduced disease-free survival (13 months), compared with the patients with no nuclear pSTAT3 expression (64 months, p = .019). Cox regression analysis revealed nuclear pSTAT3 as the most significant predictor of poor prognosis (p = .024, hazard ratio [HR] = 2.7).

Conclusions. Increased nuclear accumulation of pSTAT3 occurs in early premalignant stages and is a marker for poor prognosis of OSCC. © 2010 Wiley Periodicals, Inc. Head Neck **33**: 482–489, 2011

## Keywords: pSTAT3; STAT3; leukoplakia; dysplasia; OSCC

**O**ral squamous cell carcinoma (OSCC) accounts for a large proportion of head and neck malignancies (>40% in the United States and >90% in South-East

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Asia), and is often preceded by well-defined, oral lesions such as leukoplakia, some of which develop into frank malignancy.<sup>1</sup> Despite the fact that oral cancer sites are readily amenable to clinical examination, and thus early detection, OSCCs are detected in advanced stages; thus 5-year survival rates of OSCC have not improved >50%.<sup>2,3</sup> The limited efficacy of chemotherapy in patients with advanced-stage or recurrent disease reflects an incomplete understanding of the molecular mechanisms underlying oral tumorigenesis.<sup>4,5</sup> Leukoplakia with histologic evidence of dysplasia is associated with a high likelihood of progression to cancer; however, it is not an accurate predictor of cancer risk. Thus, there is a need for molecular markers to complement histopathologic examination for identification of high risk oral lesions in early stages. This in turn may lead to early intervention and more effective treatment of high-risk lesions. thereby reducing morbidity and mortality caused by progression to frank malignancy.

Signal transducer and activator of transcription 3 (STAT3) is a member of the STAT family, which participates in the normal cellular responses to cytokines and growth factors as transcription factors.<sup>6,7</sup> STAT3 is present in the cytoplasm under basal conditions and is activated as a consequence of ligand-mediated receptor activation provided by Janus tyrosine kinases (JAKs) or growth factor, platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF).<sup>6-8</sup> In normal cells, ligand-dependent activation of the STATs is

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