Researchers Identify Potential Prognostic Marker for Recurrence of Head and Neck Squamous Cell Carcinoma
Molecular Profiling May Be Useful for Early Diagnosis and Treatment Decisions, According to Study Published in The American Journal of Pathology

Philadelphia, PA, March 20, 2015 – A new study provides the first evidence that the mediator complex subunit 15 (MED15) may play a crucial role in the pathophysiology of head and neck squamous cell carcinoma (HNSCC). MED15 overexpression was found to be associated with higher mortality rates in HNSCC patients with cancer recurrence, particularly in oral cavity/oropharyngeal tumors, according to the study published in The American Journal of Pathology. MED15 overexpression was also associated with heavy alcohol consumption, which is an HNSCC risk factor.

HNSCC is the sixth most common cancer worldwide and has a high rate of recurrence and early metastatic disease, resulting in approximately 350,000 deaths each year. “Our findings suggest that MED15 may serve as a prognostic marker for HNSCC recurrence and as a therapeutic target in HNSCC patients suffering from recurrences,” said lead investigator Sven Perner, MD, PhD, of the Department of Prostate Cancer Research, Institute of Pathology, and the Department of Otorhinolaryngology at the University Hospital of Bonn (Germany).

Mediator is a multiprotein complex that regulates many signaling pathways. In humans, it consists of 30 subunits including MED15, which has been implicated in breast and prostate cancer, with particular attention being given to its link to transforming growth factor-β (TGF-β) signaling. “The evidence that multiple aberrant pathways account for the progression of HNSCC calls for a much deeper understanding of the effect of molecules involved in these signaling pathways upon HNSCC progression,” noted Dr. Perner.

To investigate the role of MED15 in HNSCC, the researchers analyzed tissues from 113 patients with primary tumors, 30 recurrent tumor tissues, 85 lymph node metastases, and 20 control samples of normal squamous epithelial tissue. Using immunohistochemical staining, expression scores were calculated by multiplying staining intensity by the index of immunoreactive cells and categorized as no expression...
(<0.07), low expression (≥0.07<0.2), or overexpression (≥0.2). They found that MED15 was overexpressed in 35% of primary tumors, 30% of lymph node metastases, and 70% of recurrences, in contrast to no or low expression in control samples.

To determine the extent to which MED15 levels correlated with mortality, the investigators performed immunohistochemical analysis of primary tumor tissues from the 108 patients who developed recurrent tumors. They found that the mortality rate (defined as death within 1 to 12 years after first diagnosis) increased from 58% overall to 78% in the subset of patients whose tumors showed MED15 overexpression, with a significant association found between MED15 overexpression and high mortality.

Further investigation revealed that the mortality rate of patients with tumors in the oropharynx or oral cavity was significantly higher than that of patients with tumors in the hypopharynx or larynx. Likewise, the expression of MED15 was found to be higher in oral cavity/oropharyngeal tumors compared with tumors from the hypopharynx or larynx.

The study also investigated whether MED15 levels were associated with any of the risk factors for HNSCC, such as tobacco use, alcohol consumption, or chronic oncogenic human papillomavirus infections. Only heavy alcohol consumption was found to be significantly associated with MED15 overexpression, shedding light on the possible mechanism of action of alcohol’s adverse influence.

Dr. Perner and his co-investigators believe MED15 may be a molecular marker that can be used to predict the risk for development of tumor recurrence or metastases that can help clinicians make early diagnosis and treatment decisions. Support for this hypothesis comes from their observations that in 74% of cases, there was a concordance for the presence or absence of MED15 overexpression in samples from a patient’s primary tumor and corresponding lymph node metastasis. In addition, MED15 expression correlated with high proliferative activity in HNSCC tissues and genetic inhibition of MED15 reduced both cell proliferation and migration. They also found that MED15 was highly expressed in the HNSCC malignant cell lines HSC-3 and SCC-25.

“Such observations indicate that MED15 overexpression is likely to be a clonal event in the progression of HNSCC,” explained Dr. Perner. (A clonal event is a mutation, deletion, or translocation that occurs within a tumor and recurs in a significant proportion of patients.) “These findings regarding MED15 overexpression are particularly significant, as genetic alterations that provide cells with growth advantages and metastatic potential may be present only in subpopulations of cells in the primary tumor, but increase in tissue from metastases and relapsed HNSCC tumors.” He suggests that a MED15 inhibitor may be a future therapeutic option, especially for patients with advanced disease and tumor recurrence.

### NOTES FOR EDITORS


This work was supported by the German Research Foundation (Deutsche Forschungsgemeinschaft (DFG) (PE 1179/4-1) and Rudolf-Becker-Foundation (S.P.), medical doctoral fellowship grant (BONFOR) of the Medical Faculty of the University of Bonn (A.O.), Gerok-Fellowship (BONFOR) of the Medical Faculty of the University of Bonn to MB, and grant from the German Research Foundation (Deutsche Forschungsgemeinschaft (DFG) (LE 2483/4-1) (C.L.).
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