MED15: a potential biomarker for head and neck squamous cell carcinoma?

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Keywords: diagnostic marker • head and neck squamous cell carcinoma • MED15
• mediator complex • prognostic marker • therapeutic target

The Mediator complex

The Mediator complex is an essential component of the basal transcription machinery and directly involved in the regulation of specific gene expression [1]. This multiprotein complex contains 33 subunits in humans and based on structural and functional properties can be subdivided into four modules: head, middle, tail and kinase module. While subunits from the head and middle directly bind to the RNA polymerase II, the tail and kinase interact specifically with regulatory elements from several pathways or transcription factors. Thus, the Mediator serves as an integrative link between environment-dependent signaling and the transcription of specific genes [1]. Several studies discovered genetic alterations, abnormal expression profiles and activities of distinct Mediator subunits and its correlation with malignant properties in cancer cells [2]. Based on these findings it has been suggested that Mediator subunits might serve as novel diagnostic, prognostic and predictive markers as well as therapeutic targets for the treatment of different cancer types [2].

Head & neck squamous cell carcinoma

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer type worldwide with a mean survival time of 6–12 months at advanced and metastatic stages [3]. Advanced stages at time of diagnosis as well as tumor recurrence after primary therapy are the main reasons for poor prognosis of patients [3]. Identification of genetic and molecular alterations contributing to

cancer initiation, progression and radio- and chemoresistance provides the basis for the development of prognostic markers as well as therapeutic targets. Recent advances in profiling of HNSCC tumors based on transcriptional, genomic, epigenetic and miRNA level revealed promising molecular subgroups of HNSCC and potential biomarkers [4]. However, despite HPV status, there are no validated and clinically established biomarkers that might allow diagnosis at an early stage of disease and identify patients with high risk for metastatic or recurrent cancer [3,4].

Identifying MED15 in head & neck squamous cell carcinoma

During the last few years, three Mediator subunits have been identified to be involved in HNSCC carcinogenesis. In particular, the tail subunit MED15 which is known to be an essential coactivator of the TGF- β pathway and already described in breast [5] and prostate [6] cancer, attracted attention in HNSCC research.

Recently, Ovchinnikov and colleagues identified hypermethylated CpG sites in the *MED15* promoter in saliva of HNSCC patients [7]. By screening potential methylated candidate genes in public available DNA methylation databases, they found the MED15 promoter to be hypermethylated in various cancer types, including HNSCC. Analysis of the methylation status in the 3'-CpG and 5'-CpG site of the MED15 promoter in healthy control subjects, HPV positive as well as HPV negative HNSCC patients revealed two novel methylation sites

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within the MED15 promoter region. While there was no quantitative difference in MED15 methylation between healthy and HPV-positive HNSCC patients, HPV-negative HNSCC patients possessed significantly higher methylation levels. ROC analysis of these data revealed a sensitivity of 70 and 68% as well as a specificity of 63 and 58% for the 5'-CpG and 5'-CpG region, respectively. Based on these data the authors suggest that the quantification of MED15 promoter methylation in saliva of patients might be useful as biomarker for the detection of HNSCC [7].

“Both studies provide the first evidence that the Mediator subunit MED15 is involved in the carcinogenesis of head and neck squamous cell carcinoma...”

Different aspects regarding MED15 in HNSCC have been observed by Adler and colleagues who found MED15 to be overexpressed in HNSCC, especially in recurrent tumors possessing an aggressive phenotype [8]. Concordantly with previous studies, *in vitro* experiments revealed that MED15 promotes malignant properties of cells and regulates TGF- β activity. Furthermore, MED15 overexpression in recurrent tumor tissue correlates with higher mortality of patients, and with a tumor localization associated with worse outcome. Therefore, the authors suggest that MED15 may serve as a marker for recurrent disease and prognostic marker as well as potential therapeutic target [8].

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Both studies provide the first evidence that the Mediator subunit MED15 is involved in the carcinogenesis of HNSCC, although discrepant observations have been reported. Collectively, the results of Adler *et al.* show that increased MED15 levels associate with a more aggressive phenotype of HNSCC. Additionally, high MED15 expression has been found in recurrent tumors in which MED15 overexpression correlates with higher mortality rates of patients. How-

ever, future studies upon access to tissue will have to resolve if MED15 overexpression in primary tumors correlates with the probability of developing recurrent disease. This relationship would provide evidence whether MED15 might serve as prognostic marker at time point of diagnosis and reflects the aggressiveness of the tumor. Furthermore, increasing the sample size is required to determine the exact specificity and sensitivity of MED15 as biomarker. As MED15 has been observed in several tissue types, the benefit of developing MED15 as a diagnostic biomarker in body fluids such as blood or saliva is limited in case of a tumor of unknown primary. However, MED15 as a biomarker in body fluids might be of great advantage as a marker for disease progression and recurrence. Further studies are required to determine the MED15 promoter methylation levels of different tumor types and the adjacent normal tissue. Although the results show promising evidence that MED15 promoter alterations occur frequently in HNSCC, the false-negative and false-positive rate described would require additional markers for diagnosis.

Conclusion

Collectively, further studies are needed to fully explore MED15 as diagnostic and prognostic biomarker. In addition, strategies need to be developed to assess if MED15 has the potential for the use as a predictive biomarker and as a therapeutic target.

Financial & competing interests disclosure

The University of Bonn has filed a patent that includes and is not limited to the use of MED15 in prostate cancer, on which S Perner, D Adler and A Offermann are coinventors. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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