Oxidative stress signatures are related with a mesenchymal-like phenotype and an unfavorable prognosis in a subgroup of oropharyngeal squamous cell carcinoma

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Introduction

OPSCC patients frequently develop unfavorable metastases and inoperable local and regional recurrences. HPV-positive OPSCC await a favorable prognosis in general, however, patients present with higher tendency for metastasis. Recent publications including our own work showed that a subgroup of HPV-positive OPSCC present with oxidative stress signatures and mesenchymal like phenotype (1, 2).

Material and methods

We showed in a recent study by mRNA array analysis of HPV+ OPSCC with known integration status (episomal, integrated or mixed) upregulation of known and putative components of the WNT signaling pathway and oxidative stress related gene products (2). Here, we collected 51 OPSCC samples including 28 HPV-positive cases with both FFPE and fresh frozen tissue available. Expression of key components of the EMT, retinoic acid and oxidative stress pathways including NRF2, AKR1C1/3, ALDH1A2, Frizzled 4/10, β-Catenin, E-Cadherin, Vimentin and the EMT regulatory miRNAs miR-9, miR-16-2 and miR-363 were determined by immunohistochemistry and/or RT-qPCR.

Results

We analyzed 51 oropharyngeal squamous cell carcinomas of patients treated at the Department of Otorhinolaryngology and Head and Neck Surgery of the University Hospital of Cologne, Germany, between 2004 and 2011. RNA and protein expression analysis revealed that both in HPV+ and HPV- subgroups increased oxidative stress response (NRF2, AKR1C1/3) is going along with β-Catenin activation and increased risk for relapses (χ² = 0.011). However, complete activation of the EMT pathway including Frizzled 4/10, β-Catenin, E-Cadherin and Vimentin was observed only in HPV+ OPSCC.

Conclusion

Our data show that OPSCC presenting with upregulation of oxidative stress response signatures have a higher tendency to undergo EMT. FZD4 and FZD10 are known to be regulated by 17ß-Estradiol and/or retinoic acid (3,4), which are both regulated by AKR1C1/3 (5). Furthermore, impaired ALDH1A2 expression is correlated with a mesenchymal like phenotype and unfavourable prognosis due to a misregulation of retinoic acid synthesis (6).

We therefore conclude that disturbed retinoic acid synthesis due to impaired oxidative stress signalling may lead to EMT and speculate that a subgroup of OPSCC patients at high risk for treatment failure might benefit from an adjuvant treatment with retinoids.

Literature

1. Leemans, Snijders and Brakenhoff, Nat Rev Cancer 2018
2. Huebbers et al., Int J Cancer, in print

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