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Mechanisms underlying the resistance of human papillomavirus-infected or -transformed cells to Th1 immunity

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SUMMARY

The clearance of high-risk human papillomavirus (hrHPV) infected or transformed cells requires the local presence of a strong type 1 T cell response but HPV has evolved mechanisms to resist immune attack. The Th1 cytokines IFNγ and TNFα can induce programmed necrosis (necroptosis), which is one of the mechanisms to amplify the immune response and thereby to resist viral infections. We found that hrHPV impaired IFNγ and TNFα-induced necroptosis by down-regulation the expression of RIPK3, a key component in the necroptosis pathway, in HPV+ keratinocytes. The mechanism which was responsible for down-regulating RIPK3 expression was due to HPV-induced histone methylation. The methyltransferase inhibitor DZNeP restored the expression of RIPK3 in HPV+ keratinocytes, and increased necroptosis in HPV+ keratinocytes. The Th1 cytokines IFNγ and TNFα can also mediate the growth arrest of infected keratincoytes, but hrHPV also effectively inhibited the arrest of cell growth by down-regulating IFITM1. Thus, we identified two mechanisms that may explain how the human papillomavirus itself can thrive for a long time in an immune competent host.

We also studied how HPV-induced cancers may resist the immune system. We showed that tumor infiltrating IFNγ and TNFα producing HPV16 specific T cells were present in about 65% of all HPV-associated head and neck cancers and this correlated strongly with improved survival of patients after treatment. Yet, despite the presence of such T cells in the majority of cancers, before treatment the tumor still progressed pointing at resistance mechanisms. We found that HPV16-positive tumor cells also lacked expression of RIPK3 and were not sensitive to the necroptosis induced by IFNγ and TNFα. However, this resistance could be overcome by treatment of these cancer cells with a combination of cisplatin and these Th1 cytokines, resulting in enhanced killing of tumor cells. Last but not least we revealed another possible resistance mechanism in head and neck cancer. We showed that treatment with a combination IFNγ and TNFα and the clinically applied EGFR inhibitor Cetuximab resulted in an increased gene expression of multiple cytokines, including CXCL9,

CXCL10 and CCL5, which may amplify the attraction of more lymphocytes to the tumor site. Hence, EGFR signaling in tumors dampens inflammation. We revealed that the molecules JNK and MEK1, downstream of the EGFR, played a major role in mediating the suppression of IFNγ and TNFα-mediated production of CCL5, CXCL9 and CXCL10. In addition, we found that c-RAF signaling was important for the production of CCL5, CXCL9 and CXCL10 in head and neck cancer cells.

Overall, we showed the mechanisms how Th1 immune response regulate hrHPV infection and hpv related cancer, and we also showed that hrHPV-infected and –transformed cells developed several means to dampen and/or resist the effects of Th1 immune response.