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Androgen receptor signaling mediated chronic inflammation drives sex disparity in HNSCC progression and therapy response

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Abstract

Background: Head and neck squamous cell carcinoma (HNSCC) is a highly prevalent and lethal cancers worldwide with a higher incidence in men than in women. Molecular analysis across various cancers have classified HNSCC into the group of cancers with strong sex-based effect. However, the underlying cellular and molecular mechanisms for these sex-related differences in susceptibility and therapeutic response in HNSCC is rather limited.
Chronic inflammation plays a key role in HNSCC progression and is influenced by many factors that includes sex hormone signaling which modulates both the tumor microenvironment (TME) and systemic immune responses. Recent studies have highlighted the importance of androgen receptor (AR) signaling contributing to immune suppression, increasing the tumor development and inflammatory responses in males. However, the multifaceted relationship between AR and key inflammatory mediators such as IL-1β and COX-2 (PTGS2, prostaglandin-endoperoxide synthase 2) which are crucial regulators of inflammation in HNSCC and may contribute to sex disparities, remains unexplored. Therefore, comprehensive investigations in well characterized clinical and pre-clinical models are essential to identify the sex-specific prognostic and therapeutic targets, addressing a critical unmet clinical need with significant translational impact.
Aims: This study aims to investigate the role of androgen receptor signaling in modulating inflammation within the TME and its contribution to immune suppression and tumor progression in males, with the goal of enhancing sex-specific therapeutic strategies.
Methods: In this study, we generated pre-clinical mouse models using 4-Nitro Quinoline-1-Oxide (4NQO) - a tobacco surrogate and cancer cell lines derived thereof to address the mechanism of sexual dimorphism in HNSCC. To uncover the complexity of the TME in HNSCC, we utilized spatial imaging techniques in preclinical mouse tumors. Immunohistochemistry (IHC) was used to stain for AR, COX-2 in clinical and pre-clinical tumor samples. Additionally, we evaluated the synergistic potential of AR inhibition and anti-PD1 therapy in HNSCC in pre-clinical mouse models.
Results: 4NQO exposure revealed significant sex-based differences, particularly in IL-1b wildtype (+/+), but not knockout (-/-) mice and between castrated vs. sham operated male mice, indicating role for sex hormones in HNSCC pathogenesis. Our findings suggest that COX-2 staining patterns differed by sex, with male patients showing predominant cancer cell expression, whereas in females preferentially expressed in stromal cells of TME. Spatial multiplex imaging has showed females with a robust active immune surveillance and males with more immune suppressive microenvironment. Interestingly, blocking the AR signaling with Enzalutamide in immune-competent male mice altered immune dynamics whereas no effect was observed in immune-compromised mice suggesting an immune regulatory role of AR. Finally, combination of enzalutamide with anti-PD1 led to complete tumor regression in the mice models bearing 4NQO cell line tumors. This study highlights AR signaling as a key regulator of TME in HNSCC. Hence, targeting AR may reduce inflammation driven immune suppression in males thereby enhancing the efficacy of immunotherapy in HNSCC.