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CAN THE TYPE OF ONCOGENIC TRANSFORMATION BY HUMAN PAPILLOMAVIRUSES INFLUENCE THE CHOICE OF CANCER IMMUNOTHERAPY?

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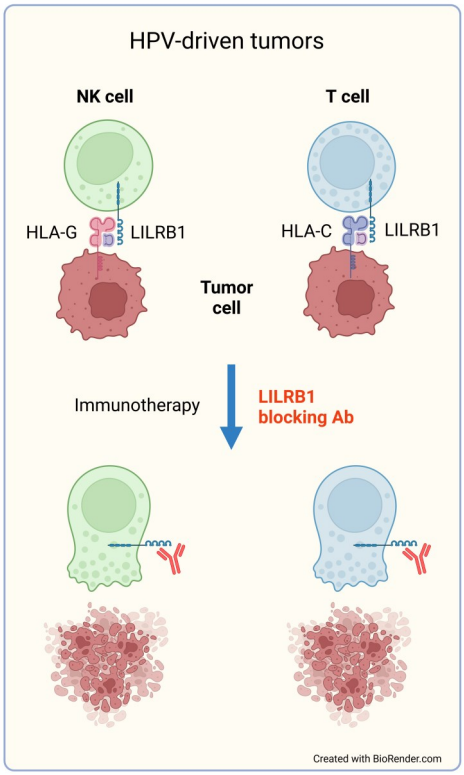
High-risk human papillomaviruses can induce malignant transformation of cells resulting in anogenital cancers, particularly cervical cancer (CC), and a proportion of head and neck squamous cell carcinomas (HNSCC). The viral E6 and E7 oncoproteins are required for the induction and maintenance of transformation and the E5 protein contributes to tumorigenesis (1). The E6 and E7 expression is usually increased after the integration of viral DNA into the host genome which is associated with inactivation of the viral E2 gene (2). In HNSCC and CC cases driven by HPV infection, an alternative tumorigenesis pathway has been described with extrachromosomal persistence of the HPV genome and higher expression of the viral E2, E4, and E5 genes (3). In addition to affecting cellular genes associated with proliferation, survival, and differentiation of infected cells, the E2, E5, E6, and E7 proteins have been shown to modify the expression of immune-related genes (4). Since antitumor immunity is a critical factor in the development of HPV-associated cancers which may also influence the efficacy of cancer immunotherapy, we analyzed the expression of immune-related genes in HPV-associated tumors with respect to the types of tumorigenesis. Transcriptomic HNSCC and CC datasets from The Cancer Genome Atlas were used for this analysis. Clustering with immune-related genes resulted in two clusters of HPV16-positive squamous cell carcinomas in both tumor types: cluster 1 had higher activation of immune responses, including stimulation of the antigen processing and presentation pathway, which was associated with higher immune cell infiltration and better overall survival, and cluster 2 was characterized by keratinization. In CC, the distribution of tumor samples into clusters 1 and 2 did not depend on the level of E2/E5 expression, but in HNSCC, most E2/E5-high tumors were localized in cluster 1 and E2/E5-low tumors in cluster 2. Further analysis did not reveal any association between the E2/E5 levels and the expression of immune-related genes. Nevertheless, it confirmed the role of components of the antigen processing and presentation pathway in HNSCC and CC survival. In addition, high expression of 11 leukocyte immunoglobulin-like receptor (LILR) genes was found in tumors with high immune cell infiltration. Since some of these receptors, that are expressed on different subsets of immune cells, are inhibitory (LILRB) and bind both classical and non-classical MHC class I molecules (5), their blockade could be used for immunotherapy of tumors with various MHC class I expression.



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