

«Immune checkpoints» and mechanisms of immune suppression in virus-associated cancer: putative contribution in the induction of invasive tumor growth (by the example of cervical cancer)

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Achieving positive outcomes of using immunotherapeutic approaches in cancer treatment implies multifaceted targeting of functionally different mechanisms of immune response, including mechanisms governed by «immune checkpoints», with the involvement of immunoregulatory (suppressive) cell populations, as well as reactions of anti-tumor innate immunity and inflammation. Of particular interest, both scientific and clinical, are molecular mechanisms that accompany the initial steps of invasive growth of a tumor and therefore can drive its progression. In the case of virus-associated cancer, particularly cervical cancer, there are still many questions to be answered regarding this issue. In the present work, transcriptomes of pre-invasive and invasive cervical cancer tissue samples were explored using RNA sequencing (RNAseq) on the Illumina MiSeq platform followed by characteristics of differentially expressed transcripts and bioinformatic analysis of up- and down-regulated immune-related signaling pathways.

According to RNAseq data, in early-stage invasive cervical cancer, the expression of a wide set of interferon-induced genes and inflammatory response genes (including chemokines and pro-inflammatory cytokines), which are known to be under the control of a specific group of innate molecular sensors of nucleic acids, was significantly elevated, as compared to pre-invasive carcinoma. In contrast, effector T- and NK-cell activation markers were expressed at low levels. Interestingly, many markers of «immune exhaustion» and inhibitory molecules of «immune checkpoints» didn't show any noticeable increase in mRNA levels, furthermore, some of them were found to have lower expression levels in invasive cancer. This may be considered a direct consequence of impaired immune cell activation processes and an essential condition for further progression of inflammatory microenvironment required for invasive growth of a tumor. Pathway analysis confirmed this assumption by revealing that among the mechanisms most significantly upregulated in invasive vs. pre-invasive cancer those mediated by immunosuppressive cytokines (for example, TGFβ, IL4) and implicated in differentiation of regulatory T cells (for example, IL2-STAT5 pathway) were prevalent, while IL12-dependent pathways of T- and NK-cell activation and differentiation were enriched among the downregulated genes. The results of comparative transcriptome analysis are in agreement with our findings from flow cytometric assessment of regulatory (suppressive) cell populations within tumor-infiltrating lymphocytes obtained by enzymatic dissociation of tissue samples. Flow cytometry was also used to characterize co-expression of PD-1/CD279, TIM-3/CD366, and LAG-3/CD223 ('immune checkpoints') in major subsets of peripheral blood lymphocytes from patients with early forms of cervical cancer. The work is supported by the Russian Science Foundation (project № 17-75-10027).