

Hypoxia manipulating infiltrating T cells in solid tumor with respect to CD5 expression

Avika Sharma & Ambak Kumar Rai*

Department of Biotechnology, Motilal Nehru National Institute of Technology Allahabad, Prayagraj 211004, Uttar Pradesh, India

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Reduced levels of oxygen in the microenvironment, defined by the term hypoxia, is a feature of the growing solid tumor. The hypoxic tumor microenvironment (TME) modulates the tumor-infiltrating lymphocytes (TILs), such as T cells, favoring tumor growth and survival. This mini-review emphasizes how hypoxia affects infiltrating CD8⁺ cytotoxic T cells and regulatory T cells (Tregs) within the TME. CD5, a T cell marker expressed by TIL and Tregs, is a negative regulator of T cell receptor (TCR) signaling. We propose two mechanisms of loss of TIL function in TME: firstly, reduction in the CD5 expression on TIL followed by activation-induced cell death (AICD). Here, our findings showed hypoxia-inducible factor-1 α (HIF-1 α) binding to the promoter of a non-conventional human endogenous retrovirus (HERV) derived alternate mRNA transcript of CD5. This results in reduced surface and increased intracellular expression of CD5 protein, a phenotype that is quite common in leukemic T cells, particularly in acute T cell lymphoblastic leukemia. Secondly, hypoxia attracts Treg cells, characterized by high CD5 levels, further suppressing TIL function. This minireview highlights an interplay between hypoxia, HIF-1 α , and CD5 and provides insights into tumor immune evasion and inefficacy of TILs.

Keywords: Hypoxia-inducible factor, Tumor microenvironment, Tumor-infiltrating lymphocytes, Regulatory T cells, Human endogenous retrovirus