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Mapping Immune Regulators in the Tumor Microenvironment of Waldenström Macroglobulinemia

Valušková Z.1*, Suroviaková K.1*, Marinkovičová M. E. 1, Zbellová L. 1, Csicsátková N.1, Drgoňa Ľ.2, Tina Bagratuni[3], Efstathios Kastritis[3], Cholujová D.1, Jakubíková J.1

[1] Cancer Research Institute, Department of Tumor Immunology, Biomedical Research Center, v. v. i., Slovak Academy of Sciences, Dubravska cesta 9, 84505 Bratislava, Slovakia;

[2]Department of Oncohematology, Comenius University and National Cancer Institute, Bratislava, Slovakia

[3]Department of Clinical Therapeutics, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece

* authors contributed equally

ABSTRACT

Introduction

Waldenström macroglobulinemia (WM) is a rare lymphoplasmacytic lymphoma characterized by clonal proliferation of IgM-expressing lymphoplasmacytic cells of the mature B lymphocyte lineage, ranging from small B cells to fully differentiated plasma cells. In WM, the immune tumor microenvironment (TME) is crucial for disease progression, involving interactions between malignant WM cells and immune cells that contribute to immune evasion, tumor growth, and resistance to therapy. Specifically, immune checkpoint molecules are implicated in the TME, facilitating immune evasion and presenting potential targets for immunotherapeutic strategies.

Methods

In this study, our pipeline was designed to characterize the expression patterns of inhibitory and costimulatory immune checkpoint molecules on different subsets of immune cells, both adaptive and innate, within the TME of bone marrow samples from patients with WM compared to age-matched healthy donors (HD) by utilizing multiparameter flow cytometry.

Results

By mapping the adaptive TME, we observed significantly lower expression of CD27, a member of the tumor necrosis factor receptor superfamily, on cytotoxic T cells in WM patients compared to HD. The CD27-CD70 axis can influence the TME by modulating immune responses, potentially leading to an immunosuppressive environment that favors tumor progression. On T cell progenitors, we observed downregulated expression of OX40 (also known as CD134 or TNFRSF4), a co-stimulatory receptor that plays a crucial role in T cell proliferation, survival, and memory formation, in WM patients compared to HD. The modulation of the OX40/OX40L axis interaction may suppress effector T cell activity and influence the development of memory T cells, thereby contributing to an immunosuppressive milieu and promoting disease relapse. By assessing innate immunity in natural killer (NK) cells, we observed a decrease in the expression of OX40, programmed cell death protein 1 (PD-1), and T cell immunoglobulin and mucin domain-containing protein 3 (TIM-3), which play significant roles in the regulation of immune responses, in WM patients compared to HD. In the TME of WM, TIM-3-mediated inhibition of NK cells can further contribute to immune evasion by malignant cells. Evaluating the adaptive T cell compartment compared to innate NK cells, we observed high expression of 2B4 on both immune subsets. T cells demonstrated higher expression of CD27 and DNAM-1, whereas NK cells showed elevated levels of TIGIT. Conversely, the expression of OX40, PD-1, TIM-3, ICOS, 4-1BB, BTLA, CTLA-4, and LAG-3 immune checkpoint molecules was lower.

Conclusions

In conclusion, the CD27-CD70 and OX40/OX40L axes might be implicated in the pathogenesis and progression of WM disease, mainly by modulating T-cell responses that can lead to T-cell exhaustion and dysfunction, whereas TIM3 could modulate NK cell function. Targeting these pathways offers a promising therapeutic strategy in WM, either by restoring T cell function or enhancing NK cell activity, thereby reinvigorating the anti-tumor immune response to improve outcomes in patients with WM.

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