DECIPHERING THE IMMUNE MICROENVIRONMENT IN WM

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Recent investigations have improved our understanding of the molecular aberrations supporting Waldenström macroglobulinemia (WM) biology: the immune microenvironment has been shown to contribute to WM. By combining in vivo transgenic murine model of human-like WM, single-cell RNA sequencing and in vitro functional studies, the role of regulatory T cells (Tregs) has been investigated. Mirroring the murine model, transcriptomic profiling of Tregs derived from patients with WM unveiled a peculiar WM-devoted messenger RNA signature, with significant enrichment for genes related to nuclear factor κB-mediated tumor necrosis factor α signaling, MAPK, and PI3K/AKT, which was paralleled by a different Treg functional phenotype. By investigating the B-cell-to-T-cell cross talk at single-cell level, the CD40/CD40-ligand axis was identified as a potentially relevant axis that supports WM cell-Tregs interaction. Taken together, these evidences demonstrate the occurrence of a Treg-mediated immunosuppressive phenotype in WM, which can be therapeutically reversed by blocking the CD40L/CD40 axis to inhibit WM cell growth.