Abstract Submission

13. Myeloma and other monoclonal gammopathies - Biology & Translational Research

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DYNAMIC INTERPLAY BETWEEN TUMOR AND MICRO-ENVIRONMENT DURING MYELOMA DISEASE PROGRESSION

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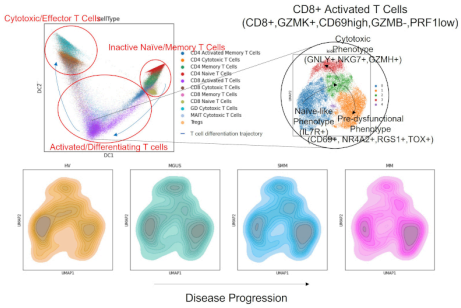
Background: Multiple Myeloma (MM) is an incurable plasma cell (PC) malignancy that evolves from two premalignant stages: Monoclonal Gammopathy of Undetermined Significance (MGUS) and Smoldering Multiple Myeloma (SMM). The disease progression has been characterized to be driven by intrinsic genomic events in the myeloma cells and by gradual dysregulation of the immune system.

Aims: We investigated how the interplay between tumor cells with their microenvironment and the underlying complex and dynamic immune biology evolve during this process.

Methods: Single cell multi-omics profiling, including RNA, B-cell receptor (BCR) and antibody barcode-tagged 10x sequencing, was conducted on human bone marrow (BM) aspirates collected at 6 Belgian centers from 4 cohorts: 31 healthy elderly and 28 MGUS, 32 SMM and 32 newly diagnosed MM. Mononuclear cell isolation, freezing and transport to central facilities was optimizedand data were integrated and filtered using Scanpy and Scirpy. The main immune cell types were identified from the RNA and antibody data using SingleR. Further functional subtyping was done using Leiden clustering. Differential pathway expression analysis was performed with Muscat and FGSEA.

Results: From the tumor cell transcriptomes, our analyses confirmed the previously documented myeloma molecular hallmarks, such as MYC and IFN-a signaling, cell proliferation, energy metabolism and oxidative phosphorylation. Evidence was found for transcriptomic similarities and within-and between-patient malignant PC transcriptomic heterogeneity, as well as the existence of multiple transcriptomic clones in several patients. We observed a positive correlation between the antigen processing mechanism in the PCs with IFN response, suggesting that this mechanism associates with initiation of the immune recognition and activation against the tumor.The gradually increasing differential gene expression was also observed in the immune microenvironment: dysregulation of signaling pathways initiates early in MGUS and spreads throughout the various cell types surrounding the tumor cells. Cell population shifts were also found. In the CD1C+ DCs, that play a role in cancer immune control, a functional shift was observed that correlated with disease progression towards a more mature and antigen presenting phenotype with higher levels of CD83, HBEGF, MCL1 and CXCL16 as well as increased TNF-a pathway. Similarly, a shift was observed in the macrophage population, toward M1 state showing high IFN response along with expression of MS4A4A, STAT1, TNFSF13B and TRAIL in more severe disease. Interestingly, in the CD8+ T cells, we detected a pre-dysfunctional subpopulation with high expression of GZMK, activation markers CD69, CCL4, CXCR4 and genes associated with T cell pre-dysfunctionality NR4A2, RGS1, TOX and TIGIT, that was found to be associated with progression (Figure). In the CD4+ cytotoxic T cells, a proportion change was observed with more severe disease.

Image:



Summary/Conclusion: With the atlas of healthy, precursor and active MM patient BM samples, we generated a comprehensive and granular view of the various cell types involved in disease progression and provide evidence for early and gradually increasing immune dysregulation and activation of oncogenic driver pathways. Our data evidence the co-divergence and reciprocal stimulation of transcriptomes of tumor and microenvironment and support the postulation of microenvironment as a central modulator of cancer cell growth, survival and metastasis.

Keywords: Monoclonal gammopathy, Multiple myeloma, Tumor immunology