Investigating the Role of the BAFF-APRIL System in Promoting Progression of Smouldering Myeloma (SMM)

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Abstract track: Plasma cell precursor and other disorders

Introduction: The BAFF-APRIL system, comprising two ligands (APRIL and BAFF) and three receptors (BCMA, TACI, and BAFF-R), is a key regulator of B-cell homeostasis and myeloma (MM) survival. To explore how the BAFF-APRIL system may regulate progression from SMM to MM we performed a ligand-receptor and pathway analysis.

Methods: We utilised our single-cell atlas (64 SMM, 64 MM and 107 healthy donors), including samples from the COSMOS trial (NCT05047107)**.** The soluble sink of the BAFF-APRIL axis was determined by ELISA analysis of sBCMA, sAPRIL, sTACI, and sBAFF protein levels in peripheral blood and bone marrow (BM) plasma of SMM (n=15) and MM (n=14) patients, and correlated with results of flow cytometry of BM immune subsets.

Results: BCMA and TACI were expressed in 60% and 40% of malignant plasma cells (PCs), respectively, being co-expressed in 33% of all PCs, while BAFF-R expression was limited to 10% of PCs. Ligand expression analysis revealed that BAFF and APRIL were expressed by CD14+ and CD16+ monocytes, granulocyte-monocyte progenitors (GMPs), and dendritic cells (DCs), confirming the myeloid compartment as the principal source of these survival signals. Interaction analysis between ligand-receptor pairs and relevant pathways revealed consistent myeloid to PC signalling in both SMM and MM. High BCMA expression was found to correlate with high TACI expression on both PCs and naive B cells. Additionally, a strong positive association was observed between BCMA expression on PCs and BAFF expression on CD14+ monocytes. Additional signalling of BAFF via cDCs was present in MM but absent in SMM. Flow cytometry analysis revealed no significant change in total frequency of either monocytes or cDCs in the BM of MM patients, suggesting a functional cellular shift rather than cell expansion.

Stratification by disease stage revealed that BCMA and TACI transcripts were significantly upregulated in PCs during progression ($p.adj < 0.001$). Similarly, APRIL and BAFF expression increased in PCs but remained stable or declined in myeloid cells. This was consistent with circulating sBCMA levels that were significantly higher in MM compared to SMM ($p = 0.01$). sTACI levels also positively correlated ($p < 0.01$) with tumour burden. Interestingly, BM sAPRIL levels were negatively correlated with tumour burden, suggesting a potential regulatory feedback mechanism.

Activation in downstream pathways of BCMA/TACI, MAPK, NF-κB, MYD88 and PI3K/AKT increased with progression, alongside increased transcript expression of members of the APRIL-BAFF axis, implying increased survival signalling via this mechanism.

Conclusion: Preliminary findings show stage-specific changes in BAFF–APRIL signalling, suggesting that malignant PCs progressively co-opt the immune microenvironment through myeloid–PC interactions and increasing cDC involvement, to support survival and disease progression. BCMA targeting may be most effective in SMM, where lower sBCMA and an ADCC-permissive immune environment support therapies.