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651.MULTIPLE MYELOMA AND PLASMA CELL DYSCRASIAS: BASIC AND TRANSLATIONAL

Transgenic Mouse Model for Translational Immunotherapy Studies on Multiple Myeloma

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Background

Genetically engineered mouse models that recapitulate key immunological features of human multiple myeloma may lend themselves to preclinical design and testing of novel immune therapies that target members of the tumor necrosis factor (TNF) receptor superfamily in addition to BCMA. One model of this sort are double-transgenic IL6Myc mice that spontaneously develop myeloma-like plasma cell tumors (PCTs) with full genetic penetrance (100% tumor incidence) and relatively short latency (4-5 months) in presence of an intact innate and adaptive immune system (Rutsch et. al. Blood 2010). IL6Myc mice exhibit serum M-spikes, respond to proteasome inhibition, and develop osteolytic lesions mimicking myeloma bone disease (Duncan K et. al. Blood Cancer J 2013, Sun F et. al. Haematologica 2020). Here, we examined changes in the immune tumor microenvironment during PCT progression in IL6Myc mice. We found that neoplastic plasma cell development was accompanied by accumulation of inhibitory T cells, T cell exhaustion, and elevated serum levels of MIP-3α and MCP-5. A subset of aberrant plasma cells expressed the TNF receptors, TACI and BAFF-R, which, together with their ligands, APRIL and BAFF, may serve as immunotherapeutic targets in myeloma not responding to BCMA-targeted treatment (Wong DP et. al. Nat Commun 2022, Braunstein M et. al. Expert Rev Hematol 2021).

Materials and methods

Double-transgenic IL6Myc mice were bred by intercrossing homozygous transgenic C.iMyc $^{\Delta E\mu}$ (Duncan K et. al. Blood Cancer J 2013) and heterozygous transgenic C.IL6 mice (Kovalchuk AL. et. al. Proc Natl Acad Sci USA 2002). Age-matched IL6Myc mice were investigated at an early (5-7 weeks), intermediate (10-12 weeks) and late (14-17 weeks) stage of PCT development using flow cytometry (Cytek Aurora) and serum cytokine levels (Bio-Plex) as main research tools.

Results

Bone marrow (BM) plasma cells, defined as CD45-gated B220 $^{-}$CD138 $^{+}$ cells, increased during PCT development, as one might have expected: 10.5 $\pm$ 5.8% and 26.8 $\pm$ 6.4% ($p < 0.05$) in early- and late-stage mice, respectively. The proportion of B220 $^{+}$CD19 $^{+}$ B cells fell accordingly: 29.6 $\pm$ 4.1% vs 5.5 $\pm$ 4.9% ($p < 0.0001$). Consistent with the notion that the BM microenvironment of PCT-bearing mice is immunosuppressive, there was a 2-fold elevation of TGF-β expressing T cells and a 4-fold elevation of IL-10 expressing T cells in the BM when late-stage mice were compared to early-stage mice. A sizeable fraction of aberrant plasma cells expressed TACI and BAFF-R in addition to BCMA (**Figure 1, left**). Spleens of IL6Myc mice undergoing tumor development contained increasing numbers of FoxP3 $^{+}$ regulatory T cells (8.6 $\pm$ 2.1% at early stage vs 14.0 $\pm$ 4.6% at late stage, $p < 0.05$) and CD11b $^{+}$Ly-6G/C $^{+}$ myeloid-derived suppressor cells (21.2 $\pm$ 9.2% vs 51.6 $\pm$ 10.1%, $p < 0.01$). Exhausted T cells, detected via expression of PD-1, TIM-3, LAG-3 and TIGIT, increased in sync with PCT progression (**Figure 1, right**). Elevated serum levels of inflammatory cytokines, including MIP-3α (95.3 $\pm$ 41.9 pg/ml in early-stage mice vs 514 $\pm$ 279 pg/ml in late-stage mice, $p < 0.01$) and MCP-5 (121 $\pm$ 43.9 pg/ml vs 284 $\pm$ 70.5 pg/ml, $p < 0.05$), agreed with flow-based tissue data.

Conclusion

Neoplastic plasma cell development in IL6Myc mice takes place in an immune suppressed tumor microenvironment similar to that promoting human myeloma. IL6Myc-driven PCTs may provide a good experimental model system for novel immunotherapeutic approaches that target TACI and BAFF-R or their ligands, APRIL and BAFF. Previous work to that end holds great promise but has been challenging thus far (Goodman DB et. al. Sci Transl Med 2022, Lee L et. al. J Immunother Cancer 2023).

Disclosures No relevant conflicts of interest to declare.

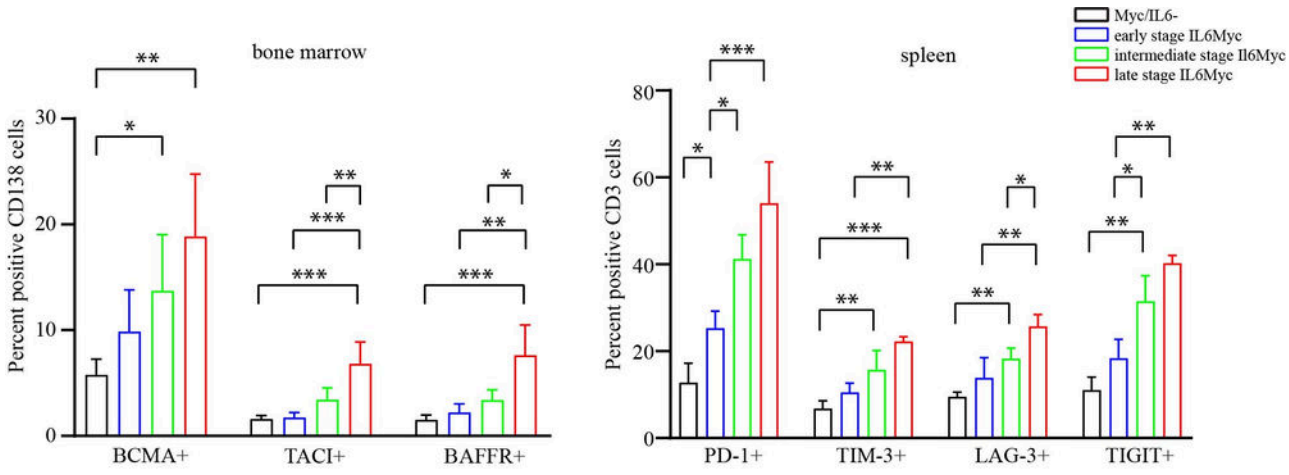

Figure 1: Expression profiling of TNF receptors on aberrant CD138 bone marrow plasma cells (left) and immune inhibitory receptors on splenic CD3 T cells (right) in IL6Myc mice at early, intermediate or late stages of PCT development. Data are presented as mean ± SD of three biological replicates. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Figure 1

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