Title: Dysregulated IL-18 critically drives immunosuppression in the multiple myeloma microenvironment.

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Summary

Tumor-promoting inflammation and avoiding immune destruction are hallmarks of cancer. Here, we demonstrate that the pro-inflammatory cytokine IL-18 is critically involved in these hallmarks in multiple myeloma (MM). Mice deficient for IL-18 were remarkably protected from Vk*MYC MM progression in a CD8⁺ T cell-dependent manner. The MM-niche derived IL-18 drove functional maturation of myeloid-derived suppressor cells (MDSCs), leading to accelerated disease progression. A global transcriptome analysis of the immune microenvironment in 73 MM patients supported the negative impact of IL-18-driven MDSCs on T cell responses. Strikingly, high levels of bone marrow plasma IL-18 were independently associated with poor overall survival in MM patients. Furthermore, our preclinical study suggested that IL-18 could be a potential therapeutic target in MM.

Significance

Using Vk*MYC preclinical models, a comprehensive analysis of the transcriptional landscape of the immune microenvironment in MM patients, and BM plasma cytokine analyses, we demonstrate that dysregulated production of IL-18 is a key driving force for immunosuppression in the MM microenvironment and a potential therapeutic target.

Conclusion: Our results reveal the critical role of IL-18 in the MM immunopathology, which provides insight into therapeutic strategies against MM.

Reference: