Modeling Inflammaging of the Bone Marrow Microenvironment Stimulates Multiple Myeloma Associated Stem Cells

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Background:
Multiple Myeloma (MM) is a malignancy of mature plasma cells, primarily affecting patients over 65, with a 5-year survival rate of ~62%. Aging alters the bone marrow (BM) microenvironment, including remodeling of the extracellular matrix (ECM), which may promote tumor-supportive functions of mesenchymal stromal cells (MSCs) and hematopoietic stem cells (HSCs). However, determining the impact of aging-related matrix remodeling on MM onset/progression remains challenging due to the absence of microphysiological systems that preserve the tumorigenic phenotype of MM cells *in vitro*. We hypothesize that recapitulating aged BM ECM may overcome these limitations by providing a physiologically relevant microenvironment that sustains MM cell behavior and models tumor-supportive functions. Additionally, we expect that interleukin-6 (IL-6), an inflammatory cytokine elevated in both the inflammaging BM microenvironment and MM, preferentially expands MM-associated MSCs without affecting HSCs.

Methods:
Cryopreserved tumor-associated MSCs and HSCs were cultured on tissue culture plastic (TCP), young ECM (≤25 y/o), or aged ECM (≥60 y/o), in either α-MEM or IMDM media, with or without IL-6. HSC cluster formation was observed, and cells were analyzed using Cytospin with Giemsa-May-Grünwald staining.

Results:
MM-derived HSCs, cultured on aged ECM, but not young, exhibited myelopoietic skewing. In contrast, young ECM supplemented with IL-6 promoted MSC expansion, suggesting a synergistic effect in developing patient-derived stromal models. Adherent MSCs were harvested and expanded on TCP to produce ECM.

Conclusion:
ECM-based microphysiological systems offer a promising, scalable approach for recapitulating aging- and MM-associated remodeling of the BM microenvironment. Understanding how aged ECM drives myeloid skewing may reveal therapeutic targets to delay/prevent MM progression. The observed myeloid bias in MM-derived HSCs cultured on aged ECM may reflect physiologically relevant disruptions in immunoregulatory cell populations. Future work will test whether ECM from MM patient-derived MSCs preserves tumor-specific phenotypes to advance translational models for MM drug discovery.