1. BIOLOGY AND PRECLINICAL

BONE MARROW MICROENVIRONMENT-DEPENDENT INDUCTION OF MTORC1 CAUSES THERAPY RESISTANCE IN MULTIPLE MYELOMA

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Multiple myeloma (MM) is a bone marrow neoplasm marked by the clonal expansion of terminally differentiated B cells. The bone marrow (BM) niche promotes drug resistance and disease progression through soluble factors and cell-cell contact. The PI3K/AKT signaling pathway, central to growth factor receptor signaling, is activated by various microenvironmental cues. We previously showed that AKT inhibition in MM cells is cytotoxic and that negative regulation of Forkhead box O (FOXO) transcription factors is a key downstream function of AKT, as FOXO activation triggers cell death and metabolic shutdown. Transcriptome analysis revealed FOXO-dependent upregulation of the Insulin-like Growth Factor-1 receptor (IGF1R) upon AKT inhibition, suggesting an adaptive pathway enabling MM cells to bypass AKT blockade. Accordingly, combined AKT and IGF1R inhibition strongly induced cell death, but this effect was lost in a humanized in vivo model including bone marrow stromal cells (BMSC). Further experiments showed that BMSC-derived soluble factors activate mechanistic Target of Rapamycin Complex 1 (mTORC1) in parallel. The mTORC1 inhibitor Rapamycin overcame microenvironment-induced resistance to AKT and IGF1R inhibitors, identifying mTORC1 activation as a critical mediator of BMSC-driven drug resistance. mTORC1 inhibition also reversed BMSC-mediated resistance to the proteasome inhibitor Carfilzomib, indicating a generalized mechanism. Conditioned medium from HS5 but not HS27a BMSC cell lines abrogated cytotoxicity of AKT/IGF1R inhibitors. Transcriptome analysis revealed differential expression of secreted factors between HS5 and HS27a, including IL-6, FGF2, and GM-CSF. Although IL-6 is a known MM growth factor, IL-6 neutralization only partially restored drug sensitivity, suggesting that additional soluble mediators contribute to resistance. Inhibition of Janus kinases (JAK) prevented BMSC-induced resistance. Preliminary data indicate this effect is independent of the canonical downstream target STAT3, suggesting a direct role of JAK in mTORC1 activation. To identify additional drivers of mTORC1-dependent resistance, we conducted whole-genome CRISPR screens in MM cell lines carrying a fluorescent mTORC1 reporter exposed to BMSC-conditioned medium. Candidate genes are now being validated using neutralizing antibodies, CRISPR editing, and pharmacological inhibition. Future work will define their roles in BM microenvironment-driven resistance.