Summary

Tumor cell-intrinsic and microenvironmental functions of PIM kinases in multiple myeloma

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Multiple myeloma (MM) is a plasma cell malignancy driven by complex genetic and microenvironmental interactions, for which there is currently no cure. This thesis investigates the dual role of PIM kinases in MM biology - within malignant plasma cells and their bone marrow niche. Transcriptomic, proteomic, and single-cell analyses demonstrated that *PIM1*, *PIM2*, and *PIM3* are overexpressed in MM, with *PIM2* being the most dominant paralog. High *PIM* expression correlated with adverse prognosis. Functional studies revealed that pharmacologic inhibition of PIMs with the small-molecule compound MEN1703 induced apoptosis and suppressed proliferation of MM cells *in vitro* and *in vivo*, including patient-derived samples. Genetic knockdown of all three PIMs recapitulated these findings, confirming their essential role in myeloma cell survival. Mechanistically, PIM inhibition impaired MYC and E2F1 transcriptional programs, reduced mTOR activity, and suppressed multiple DNA repair pathways. Importantly, MEN1703 retained its efficacy in the presence of stromal cells and synergized with proteasome inhibition. This study also identifies a tumor-extrinsic role of PIMs in MM endothelial cells (MMECs). MMECs expressed high levels of PIM1 and PIM3. MEN1703 treatment disrupted angiogenic function, actin cytoskeleton dynamics, and tumor-supportive signaling in ECs. Blocking PIMs in ECs also diminished their paracrine support of myeloma cells. Together, these results support PIM kinases as actionable targets in MM. Combined inhibition of PIM activity in both tumor and stromal compartments may represent a rational therapeutic strategy. These findings support the clinical development of PIM-targeting therapies and open future directions including biomarker-driven patient stratification and rational combination regimens in MM.