Targeting plasma cell dyscrasias in their bone marrow microenvironment.

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Waldenstrom's macroglobulinemia (WM) and multiple myeloma (MM) tumor cells are distinguished by immunophenotyping and clinical features, yet both home in the bone marrow (BM) milieu. We have demonstrated the key role of the BM microenvironment in promoting the growth and survival of MM cells, via their paracrine (cytokine-mediated) or juxtacrine (cell adhesion molecule-mediated) interaction with the BM stroma. This cardinal role of the BM milieu in MM is validated by pre-clinical and clinical anti-MM activity of the proteasome inhibitor PS-341 and the immunomodulatory thalidomide derivative (IMiD) CC-5013, which represent a new therapeutic paradigm targeting both MM cells, and their BM microenvironment. These agents have already yielded durable objective clinical responses in relapsed refractory MM patients, in the settings of a phase II trial of PS-314 (P.G. Richardson et al., ASCO 2002) and a phase I trial for CC-5013 (P.G. Richardson, et al. Blood, in press). This exciting progress in bed-to-bedside research in targeting the BM microenvironment has also provided the rationale for similar translational studies in WM, since the BM milieu can also play a key role in the pathophysiology of WM. Our pre-clinical studies of PS-341 in WM have confirmed that PS-341 induces growth arrest/apoptosis of WM cells, including both the WM-WSU cell line model and tumor cells freshly isolated from WM patients. PS-341-induced apoptosis is associated with decreases in NF-kB activity and levels of intracellular inhibitors of apoptosis (IAPs). Molecular profiling studies indicate that PS-341 induces co-ordinated transcriptional and proteomic responses, which converge to abrogate the function of key signaling cascades implicated in tumor cell growth and survival. Beside the effect of thalidomide and IMiDs on angiogenesis, tumor cell adhesion and immune effector cell function, IMIDs trigger modest growth arrest of WM cells. These results, along with previously reported responses of WM patients to thalidomide (M.A. Dimopoulos, JCO, 2001), provide the rationale for future clinical trials of IMiDs to improve the outcome of WM patients. Importantly, the anti-WM activity documented for both IMiDs and PS-341, coupled with the documented *ex vivo* synergy of these 2 agents against MM cells (Mitsiades N. et al. Blood 2002) provide the framework for combination therapy of these 2 agents, in plasma cell dyscrasias, including MM and WM.