treated HIV infection are already in progress, but the existence of an animal model that recapitulates HIV-associated vascular and thrombotic disease will be invaluable for preclinical testing of future interventions.

The fact that D-dimer elevations are observed in both pathogenic SIV and HIV infections might also suggest a potential role for anticoagulant therapy. However, it remains unclear whether the hypercoagulability associated with pathogenic SIV and HIV infections is a cause of cardiovascular disease or simply a surrogate marker for monocyte activation, which may drive cardiovascular disease through atherosclerosis and plaque instability. Because D-dimer elevations predict subsequent thromboembolic disease in HIV-infected individuals, it is plausible that the hypercoagulability observed in pathogenic SIV and HIV infections is clinically significant and potentially capable of contributing to the risk of myocardial infarction. This hypothesis could potentially be tested experimentally in the pigtail macaque model.

In summary, the studies by Pandrea et al are an excellent example of how animal models are being adapted to address the new clinical challenges facing the HIV-infected population and have the potential to accelerate the development of interventions to further reduce morbidity and mortality in this setting.

Conflict-of-interest disclosure: The author declares no competing financial interests.

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M ore than 70% of patients with MM either present or eventually develop osteolytic bone disease and despite recent advances in the treatment of MM, osteolytic bone disease remains a tremendous source of morbidity. Bisphosphonates remain a mainstay of therapy and while they reduce, but do not eliminate, the progression of MM bone disease, they are inconvenient to administer and are associated with some serious complications including jaw osteonecrosis, microfractures, and renal injury. Clearly there is room for improvement in our therapeutic arsenal for this devastating complication. To design better therapeutics for MM bone disease, one must dissect the intricate interplay between key cellular elements of the bone marrow microenvironment on which malignant plasma cells depend for their survival. This bone marrow milieu is composed of bone marrow stromal cells, osteoblasts, osteoclasts, and endothelial cells as well as extracellular matrix proteins, all of which enable the survival of MM cells as well as their cellular homing, growth, and drug resistance. Of all the osteoclast-stimulating factors secreted by MM cells, CCL3/MIP-1α is believed to play one of the most crucial roles. CCL3/MIP-1α, a small protein of the chemokine family, enables leukocyte homing to sites of inflammation or tissue injury by binding to several membrane-bound G-coupled receptors, in particular CCR1 and CCR5. While several chemokines can bind to CCR1 and CCR5, CCL3/MIP-1α is the only chemokine that has been consistently observed to be expressed and secreted in most MM cell cultures, primarily MM bone marrow, and even patient serum samples where it correlates with the extent of lytic bone lesions. MM cells produce CCL3/MIP-1α under the control of the fibroblast growth factor receptor (FGFR3) and downstream RAS-MAPK signaling, making CCL3 and its effectors tantalizing targets in patients who harbor either the t(4;14) translocation, resulting in FGFR3 overexpression, or the more commonly found activating RAS mutations. But even in the absence of these genetic changes, CCL3/MIP-1α can also be produced by other cells in the MM bone marrow microenvironment, such as osteoclasts, osteoblasts, and stromal cells. CCL3/MIP-1α induces osteolysis through the activation of specific receptors such as CCR1 and CCR5 found on osteoclastic precursors as well as mature osteoclasts. Previous attempts at blockade have included the use of cumber- somely neutralizing antibodies to CCL3/MIP-1α as well as pharmacologic inhibitors of CCR1 and CCR5. Before the current study, it was generally believed that for complete CCL3/MIP-1α blockade, both receptors would have to be targeted. Furthermore, exclusive CCR1 or CCR5 blockade in preclinical models showed that while both appear to have profound antosteolytic activities, only CCR1 inhibition could reduce tumor burden.

Here, Dairaghi and colleagues counter the notion that to achieve clinical efficacy, both CCR1 and CCR5 need to be inhibited. They use a mouse–active orally bioavailable structural analog of a CCR1-inhibiting compound already in clinical trials for inflammatory diseases. They demonstrate that CCX721 is an extremely potent and highly selective inhibitor of CCR1 function in both mouse and primary human monocytes. After PK studies, an optimal oral-dose regimen was determined and

LYMPHOID NEOPLASIA

CCR1 blockade and myeloma bone disease

Michael Sebag  McGill University

In this issue of Blood, Dairaghi and colleagues demonstrate the efficacy of a potent and orally bioavailable inhibitor of CCR1, one of the receptors for the chemokine CCL3/MIP-1α, in a mouse model of multiple myeloma (MM) and MM bone disease. They show CCX721 to be a highly selective and efficient inhibitor of CCR1 and in turn a suppressor of osteoclastastic activity, osteolytic lesions, and disease burden in a preclinical MM model.1

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used on a mouse model that has shown therapeutic fidelity in MM bone disease. CCX721, administered either prophylactically or therapeutically, reduced tumor burden in their model, as demonstrated by a reduction in a monoclonal immunoglobulin biomarker and by green fluorescent protein–tagged cell imaging. Interestingly, the reduction of tumor burden was not due to a direct cytotoxic effect on MM cells, as CCX721 had no effect on the viability of cultured mouse and human MM cell lines, no effect on subcutaneously implanted plasmacytomas and no effect on splenic MM cells in their mice. The effect of CCX721 on MM tumor burden is therefore entirely dependent on the bone marrow microenvironment. Within this environment, the authors demonstrate a marked reduction of osteoclasts and this translates into a reduction in the number osteolytic bone lesions. To suggest potential clinical efficacy in humans, they note that nanomolar concentrations of CCX721 were sufficient to effectively inhibit osteoclastogenesis from normal human mononuclear precursors. These results represent a clear improvement over those seen with other CCL3/MIP-1α inhibitors and use a molecule that is orally bioavailable and whose parent compound is already in clinical trials for inflammatory diseases.

While CCR1 inhibition may seem like an excellent idea in mouse models of diseases, human clinical trials have not been so successful. In the inflammatory diseases, 3 trials of 3 separate CCR1 inhibitors did not show much therapeutic benefit, possibly because of chemokine family cross-talk or low levels of CCR1 inhibition. In MM, Dairaghi and colleagues have shown that exclusive, but profound, CCR1 inhibition is enough to achieve clinical efficacy in their model, suggesting that any chemokine redundancy may not matter. Their work paves the way for human clinical trials of their compound, or its parent, in treating MM bone disease. However, given recent reports that the standard-of-care bisphosphonate, zoledronic acid, not only reduces the number of circulating neutrophils, anti–Gr-1 treatment was associated with an almost complete inhibition of neutrophil entry into inflamed tissues. Investigating this more closely, they observed similar effects using the Ly6G-specific antibody 1A8, which caused a striking reduction in neutrophil infiltration in a model of arthritis, without depleting circulating neutrophils. 1A8 was even able to reduce joint inflammation therapeutically when administered at the peak of the response. These findings indicate that antibody ligation of Ly6G had the unexpected effect of inhibiting neutrophil recruitment. In investigating the mechanism of this response, the authors excluded effects on neutrophil apoptosis or initial chemokine receptor signaling. In contrast, they observed that anti-Ly6G reduced the ability of neutrophils to respond to chemotactic stimuli. To explain this finding, they used confocal microscopy, coimmunoprecipitation, and fluorescence lifetime imaging to generate evidence of a direct association between Ly6G and the α/β integrins and indicate that Ly6G may act to control surface levels and function of these molecules. These effects were not associated with traditional readouts of neutrophil activation, such as L-selectin shedding, although they did require an intact Fc portion of the antibody. Together these studies demonstrate a novel association between Ly6G and neutrophil α/β integrins and indicate that Ly6G may act to control surface levels and function of these molecules.

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Has Ly6G finally found a job?

Michael J. Hickey Monash University

In this issue of Blood, Wang et al reveal that ligation of Ly6G on murine neutrophils inhibits neutrophil recruitment, providing the first evidence of a function for this molecule.1

Gr-1, and more specifically RB6-8C5, the monoclonal antibody that recognizes Gr-1, has been a very important tool for immunologists investigating neutrophil function in murine models. RB6-8C5 binds to 2 members of the Ly6 family of leukocyte–expressed markers, Ly6C and Ly6G. These molecules are small GPI-linked proteins on the surface of mouse neutrophils.2 The discovery that high doses of RB6–8C5 are very effective at removing neutrophils from the circulation gave researchers a convenient and reproducible approach for assessing the contribution of neutrophils to experimental models of inflammation.3,4 More recently, since the advent of highly sensitive forms of in vivo confocal imaging, anti–Gr-1, administered at much lower non-depleting doses, has been an equally useful tool for labeling endogenous neutrophils, enabling intravital microscopy–based assessment of their behavior in vivo.5,6 However, while evidence is emerging of a role for Ly6C in controlling homing of CD8+ T cells, little if anything is known about the actions of Ly6G. So the question arises, what does this molecule do?

Wang et al did not set out to discover the role of this molecule either, but to investigate the effects of submaximal neutrophil depletion. To their surprise they observed that at low doses that did not markedly alter the number of circulating neutrophils, anti–Gr-1 treatment was associated with an almost complete signaling in multiple myeloma. Blood. 2006;108(10):3465-3471.


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