bone involvement, but it is uncertain whether this is a primary or secondary phenomenon.[4] Adipocytes are significant players in bone metabolism, but little is known about the interactions between Gaucher cells and fat cells and how they might influence bone mineralization. Altered glucose metabolism, insulin resistance, and abnormal adiponectin levels that may affect bone mineralization have been reported in untreated GD1 patients, but their clinical importance is unclear. Increased blood levels of macrophage-derived osteoclastogenic cytokines MIP-α and MIP-β may also contribute to both general and focal GD1 skeletal manifestations.[5]

As to myeloma and lymphoma, hypotheses have focused on the sphingolipid storage process itself as contributory to chronic antigenic stimulation or as an autocrine and/or paracrine stimulus to the production of cytokines and cellular growth factors.[1] Abnormal T-cell lectin responses and decreased numbers of CD4, NK, and dendritic cells have been reported.[6] Gaucher cells, characterized as alternatively activated macrophages, may secrete IL-10, a cytokine linked to development of osteopenia and myeloma. Other proinflammatory cytokines that influence bone homeostasis, B-cell differentiation, and plasma cell growth are variably abnormal in GD1 patients.[5] Proinflammatory macrophages that are recruited by and cluster with Gaucher cells are a likely source, but involvement by other cells is theoretically possible.

Mesenchymal stromal cells (MSCs) are nonhematopoietic stem cells with the capacity for self-renewal as well as differentiation into various connective tissue cells including osteoblasts and fat cells. Age-related MSC dysfunction has been related to osteoporosis, and an infusion of MSCs causes T-cell, NK-cell, and dendritic cell depletion.[7] The report of Campeau et al offers preliminary evidence that MSCs contribute to GD1 pathology. The authors studied cultured bone marrow MSCs from a GD1 patient who relapsed after an 18-month treatment interruption. Although GD1 MSCs were in many ways indistinguishable from normal cells, there was a 3-fold increase in cellular glucosyl ceramide and a marked increase in COX-2, prostaglandin E2, IL-8, and CCL2. A similar alteration in the cytokine and prostaglandin pattern was observed when normal MSCs were treated with conduritol-B-epoxide (a potent, noncompetitive glucocerebrosidase inhibitor).

The authors speculate that the glucocerebrosidase-deficient MSC secretome may be relevant to the skeletal and neoplastic anomalies associated with GD1. MSC may home to sites of bone microinjury and, via a strong multicytokine signal, recruit monocytes and stimulate osteoclastogenesis resulting in osteolytic lesions and generalized bone mineral loss. CCL2 is also a chemoattractant for normal and malignant plasma cells that may be recruited to a marrow environment where exposure to Gaucher cell–derived IL-10 (another cytokine related to myeloma and possibly up-regulated by MSC-secreted PGE2) creates a milieu conducive to malignant proliferation. Parenthetically, IL-17, a cytokine known to be increased in GD1 patients and that is associated with inflammation, bone resorption, and myeloma, stimulates the proliferation of human MSCs.[8]

Hughes[1] recently noted the limits in our current knowledge of the pathogenesis of GD1, and posited that "only hypothesis generation beyond current paradigms will allow more complete understanding and ultimately rational intervention for the diverse aspects of this disorder." The work presented by Campeau et al fits this prescription, but it is based on material from a single patient. GD1 phenotypes are notoriously heterogeneous. Many more patients will need to be studied before "the skies are not cloudy all day."

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

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● ● ● IMMUNOBIOLOGY

Comment on Ishii et al, page 3244

Orchestration of macrophage polarization

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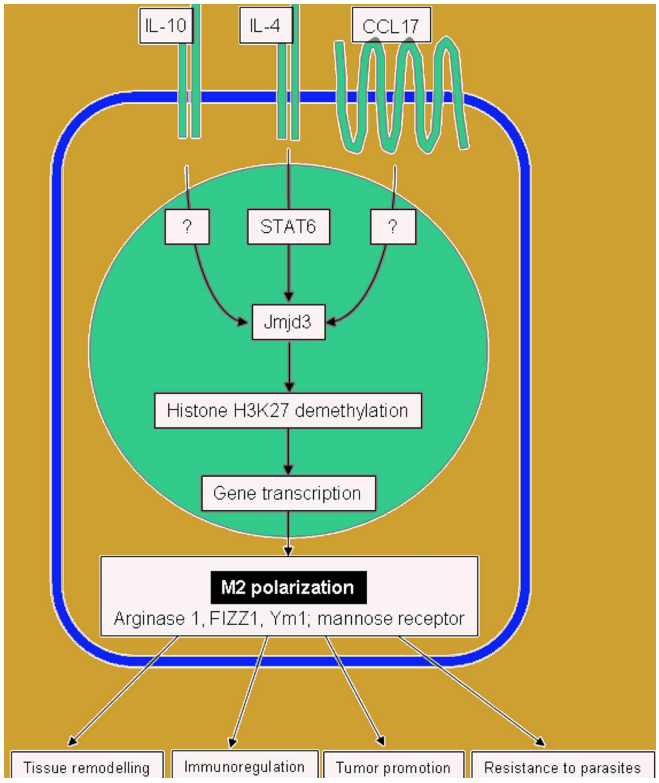
In this issue of *Blood,* Ishii and colleagues shed new, fresh light on molecular mechanisms underlying one form of macrophage activation.

Macrophages are a key element in the orchestration of tissue remodeling and repair and in resistance against pathogens. Macrophages undergo diverse forms of activation in response to cytokines and microbial signals. In particular, IFNγ and IL-4 activate distinct functional programs in mononuclear phagocytes, inducing an M1 (or classic) and M2 (or alternative) form of activation, which mirror the Th1/Th2 dichotomy.[1-3] Indeed, polarized M1 and M2 macrophages are extremes of a spectrum in a galaxy of functional state.[1,3,4] M1-polarized macrophages mediate resistance to intracellular pathogens, tissue destruction, and antitumor resistance. In contrast, M2-polarized cells come in different flavors and are generally oriented to tissue remodeling and repair, resistance to parasites, immunoregulation, and tumor promotion.

Molecular mechanisms underlying macrophage polarization remain largely undefined. Tuning of NF-κB activation by p50 homodimers has been associated with M2 differentiation.[5] PPARγ agonists have been shown to induce M2-like differentiation,[6]



Schematic representation of the role of the histone demethylase Jumonji domain containing 3 (Jmjd3) proteins in macrophage alternative polarization.

and the phosphatase SHIP was shown to play a key role in balancing macrophage polarization, although recent evidence suggests that it may act indirectly through the regulation of IL-4 production by basophils.[7]

In this issue of *Blood*, Ishii and colleagues identify a molecular pathway responsible for epigenetic regulation of key M2-associated genes in the mouse (see figure).[8] IL-4 up-regulates the histone demethylase Jmjd3 via the transcription factor STAT6. Jmjd3 contributes to demethylation of histone H3 at lysine 27, thus unleashing promoters of M2 marker genes (arginase 1, Ym1, FIZZ1, mannose receptor). As discussed by Ishii and colleagues, these results nicely parallel recent evidence, indicating that chromatin remodeling also plays a role in the control of expression pattern of specific genes in polarized Th lymphocytes.

This report opens new perspectives and raises new questions. Macrophages undergo diverse M2-like activation states in response to different signals,[1,2,4] and the role of regulation by Jmjd3, and more in general histone methylation, in these processes remains to be elucidated. Even for the IL-4–induced "alternative" M2 form of activation it is still not known whether the pathway described here accounts for the whole transcription regulation associated to it. Furthermore, FIZZ1 and arginase 1 are not induced by IL-4 in human macrophages.[9] It will therefore be important to investigate the importance of regulation of histone methylation in cells of human origin. Finally, Jmjd3 had previously been shown to be induced in a macrophage cell line by lipopolysaccharide,[10] indicating that chromatin remodeling might play a role in macrophage biology beyond alternative activation. With these open questions in mind, the new data offer a novel mechanistic insight into macrophage polarization and may pave the way to its targeting and tailoring.

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VASCULAR BIOLOGY

Comment on Suzuki et al, page 3352

Can RAP save your brain?

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In this issue of *Blood*, Suzuki and colleagues report that the bleeding complications associated with thrombolytic therapy after ischemic stroke might be counteracted by RAP, the receptor-associated protein that inhibits ischemia-induced LRP, a signaling receptor for t-PA.

Stroke is still one of the major causes of death and disability worldwide. Despite decades of clinical research, the therapeutic value of neuroprotective agents that can limit damage to the postinfarct neuronal tissue is limited.[1] The only highly effective treatment is a fast reperfusion of the ischemic brain tissue through dissolution of the culprit blood clot using thrombolytic agents. Based on a landmark study from the National Institute of