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## Myeloma wrecks Treg?

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donor receives a transplant. A shortage of well-matched donors, delays in finding them, and lengthy work-ups are all causative factors.<sup>5</sup> Cord blood transplantations and haploidentical T-cell–depleted donors can help some of these patients. The NIMA–mismatched sibling or offspring donor should not be forgotten, either. ■

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## NEOPLASIA

Comment on Prabhala et al, page 300

# Myeloma wrecks T<sub>reg</sub>?

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Multiple myeloma is associated with a deranged immune system, which is thought to be attributed to myeloma infiltration and interference of the bone marrow. Now, Prabhala and colleagues show that dysfunctional T<sub>reg</sub> cells might also contribute to the abnormalities.

Both T- and B-cell abnormalities have been demonstrated in patients with multiple myeloma (MM).<sup>1,2</sup> Consistent findings include suppressed uninvolved immunoglobulin, low CD4<sup>+</sup>/CD8<sup>+</sup> T-cell ratio, and T-cell expansion in both CD4<sup>+</sup> and CD8<sup>+</sup> T-cell subsets. In addition, a lower expression of T-cell receptor/CD3-associated signaling molecules, such as PKC- $\alpha$ , the presence of activated (HLA-DR<sup>+</sup>) T cells, and a bias towards induction of a type-2 T-cell response were reported in myeloma patients. Thus, T-cell abnormalities in MM involve changes in the number and activation status of T-cell subsets, as well as in their functions. Although the mechanisms underlying these abnormalities are unknown, it was thought that the presence of myeloma cells in the bone marrow, where human hematopoiesis takes place, was partly responsible.

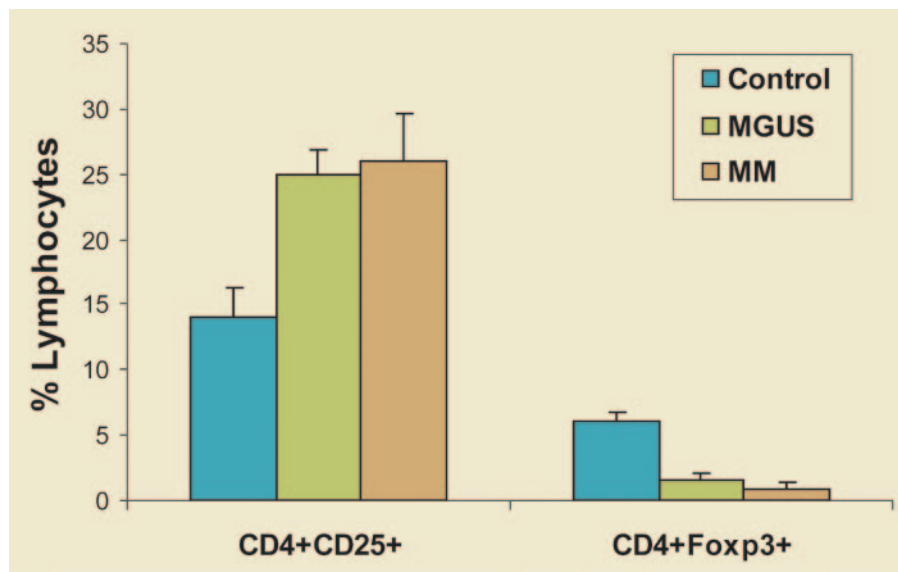
The existence of suppressive or regulatory T cells was proposed in the early 1970s, disputed for many years, and abandoned thereafter. Finally, in 1995, Sakaguchi and colleagues reported that they had identified suppressor T cells as CD4<sup>+</sup>CD25<sup>+</sup> T cells.<sup>3</sup> Eight years later, it was discovered that Foxp3 is specifically expressed in suppressive or regulatory CD4<sup>+</sup>CD25<sup>+</sup> T cells.<sup>4</sup> T regulatory (T<sub>reg</sub>)

cells play an important role in the maintenance of self-tolerance and control of autoimmunity, regulation of T-cell homeostasis, and modulation of overall immune responses against infection and tumors. In this issue of *Blood*, Prabhala and colleagues show that, although the percentage of CD4<sup>+</sup>CD25<sup>+</sup> T cells was increased in patients with MM or monoclonal

gammopathy of undetermined significance (MGUS) compared with healthy donors, the numbers of CD4<sup>+</sup>Foxp3<sup>+</sup> T<sub>reg</sub> cells were significantly decreased in these patients (see figure). Moreover, purified CD25<sup>+</sup> T cells from MM and MGUS patients were unable to suppress in vitro anti-CD3 antibody-induced T-cell proliferation, even when added in high proportions. Therefore, the investigators concluded that the number and function of T<sub>reg</sub> cells were decreased in MGUS and MM, which might, at least in part, account for the nonspecific increase in CD4<sup>+</sup>CD25<sup>+</sup> T cells and dysfunctional T-cell responses seen in these patients.

This study is important because it identifies T<sub>reg</sub> cells as one of the potentially important mediators of immune dysfunction in MM. Furthermore, the same phenomenon was also found in patients with MGUS, suggesting that these T cells may play a role in an early stage of the disease, and monitoring T<sub>reg</sub> cells at different stages of the disease may provide insight into the immune mechanisms associated with disease development and progress. Moreover, a better understanding of the function of T<sub>reg</sub> cells will also help develop effective immunotherapy for MM.

This study raises several questions for future studies. For example, what causes the decreased number and dysfunction of T<sub>reg</sub> cells in patients? One possibility is myeloma cells, which not only physically occupy the bone marrow and damage hematopoiesis, but also secrete cytokines that can impair the



Numbers of CD4<sup>+</sup>CD25<sup>+</sup> and CD4<sup>+</sup>Foxp3<sup>+</sup> T cells in MM and MGUS. Shown are the percentages of lymphocytes expressing these molecules from healthy blood donors and patients with MGUS or MM.

number and function of T<sub>reg</sub> cells.<sup>5</sup> Another question is why are there no hyperactive myeloma-specific T cells in patients, and why is it still difficult to immunize patients against myeloma antigens when suppressive T<sub>reg</sub> cells are deficient? Finally, will purified T<sub>reg</sub> instead of CD25<sup>+</sup> T cells from patients also be unable to suppress T-cell responses in vitro? We anxiously await answers to these questions. ■

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## NEOPLASIA

Comment on Dasmahapatra et al, page 232, and Gao et al, page 241

# ROS 'n' roll: a bunch of JNK?

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Two small molecule combinations that induce leukemic cell apoptosis have disparate molecular mechanisms but converge in induction of reactive oxygen species and activation of c-Jun N-terminal kinase (JNK).

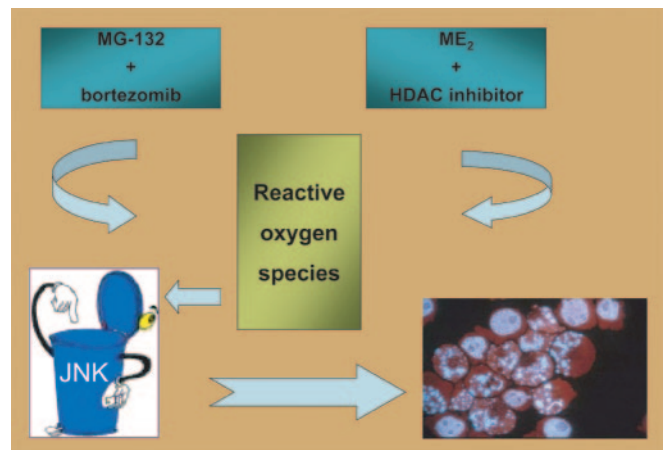
Despite the fundability of the catch phrase, to date few truly “targeted therapies” have been successfully developed for the treatment of leukemia. Effectively targeted therapy capitalizes on a significant biologic differential between malignant cells and their normal counterparts, providing a robust therapeutic index and diminishing toxicity. Unfortunately, our understanding of how leukemic stem cells differ from normal hematopoietic stem cells remains limited. Development of effective targeted therapies therefore requires some degree of serendipity in discovery of drugs or combinations that kill malignant cells with a high degree of specificity.

Steven Grant's laboratory has a long productive history of dissecting signaling pathways in leukemic cells and perturbing these pathways pharmacologically to achieve targeted apoptosis. In 2 articles in this issue, Grant and colleagues present 2 novel, apparently unrelated drug combinations, both of which demonstrate significant promise for the targeted killing of leukemic cells. Dissection of the pathways leading to apoptosis reveals convergence at activation of c-Jun N-terminal kinase (JNK).

In one article, Dasmahapatra and colleagues investigate interaction between a tyrosine kinase inhibitor adaphostin and proteasome inhibitors. Both classes of agents inactivate the Akt pathway, activating the JNK pathway through reactive oxygen species (ROS)-related mechanisms. Adaphostin and proteasome inhibitors induce apoptosis in leukemic cell lines synergistically. The combination, but not the individual drugs, induced increases in JNK phosphorylation, decreased MEK1, phospho-MEK, Raf-1, and phospho-ERK (but surprisingly little inactivation of Akt). The combination of adaphostin with either MG-132 or bortezomib led to increased generation of ROS. Apoptosis could be abrogated by addition of a free radical scavenger, which also pre-

vented JNK activation. Expression of a dominant-negative c-Jun mutant or addition of a JNK inhibitor led to resistance to the drug combination, suggesting a central role of JNK activation for the activity of this combination (Figure). Finally, the combination effectively induced cell death in primary specimens of acute myeloid leukemia (AML) blasts associated with JNK activation, but was not toxic to normal CD34<sup>+</sup> cells.

In the second study, Gao and colleagues combined a nonestrogen receptor-binding estrogen metabolite, 2-methoxyestradiol (ME<sub>2</sub>), with histone deacetylase inhibitors (HDACi's). ME<sub>2</sub> generates ROS, activates JNK, and is apoptogenic. HDACi's have diverse molecular effects, which include generation of ROS. In U937 cells, ME<sub>2</sub> plus the HDACi's sodium butyrate (NaB) or suberoylanilide hydroxamic acid (SAHA) induced apoptosis synergistically. The combination, but not individual molecules, reduced phosphorylated Akt and increased activated JNK. Akt inactivation and JNK activation preceded caspase activation and apoptosis; changes in the signaling pathways were caspase-independent. The drug combination potently induced oxidative damage; apoptosis was antagonized by the addition of a superoxide dismutase analog and by catalase. Constitutive expression of activated Akt abrogated the effects of the drug combination with the exception of oxidative injury; thus, ROS generation was presumed to be upstream of the signaling pathway changes. A pharmacologic JNK inhibitor and JNK1 siRNA diminished apoptosis in response to



Treatment of leukemic cells with combinations of a tyrosine kinase adaphostin and proteasome inhibitors or an apoptogenic estrogen-derivative ME<sub>2</sub> with HDACi's induce ROSs. This leads to activation of JNK, culminating in caspase activation and apoptosis.