Hypothesized tolerizing mechanism of IgG. Conserved T-cell epitopes in IgG that engage nTregs have been discovered. The authors hypothesize that antibody-derived T epitopes (dark blue epitope) activate Tregs, leading to suppression of effector T cells that recognize effector epitopes (red epitope), like those of IgG hypervariable regions to which central tolerance does not exist. Whether this suppression is mediated by regulatory cytokines alone, or whether contact-dependent signaling also plays a role, has yet to be determined. See the complete figure in the article beginning on page 3303.

**REFERENCES**

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**Comment on Zöllinger et al, page 3403**

**Need akt? Some myelomas do**

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The signaling pathway vivisection of MM by Zöllinger and colleagues has elegantly isolated the Akt pathway using specific genetic and pharmacologic inhibitors and shown that some but not all MM are critically dependent on akt signaling.

Tumor cells are helpful, it is not possible to duplicate in vitro the complex microenvironment of a human bone marrow. Myeloma cell lines are useful tools for discovery, but they differ significantly from primary tumor cells. Not only are they much more proliferative, but they also contain a variety of additional genetic changes, some of which are quite uncommon in primary patient tumors (eg, mutational inactivation of PTEN). Finally, the authors have not performed xenograft studies, in which the same cell lines that are responsive in vitro are grown and treated in immunodeficient mice. These studies would not have helped to define the role of the Akt pathway in MM, the main point of this paper, but would have spoken to the...
Unlocking the dysplasia puzzle

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In this issue of Blood, Zhou and colleagues describe preclinical results in vitro and in vivo, showing constitutive TGF-β activation in MDS and enhanced hematopoiesis following inhibition of TBRI kinase in MDS.

These investigators have previously shown that p38 MAP kinase regulates stem cell apoptosis in human hematopoietic failure.1 Moreover, a small-molecule inhibitor, SCIO-463 of the p38 MAP kinase pathway, improves hematopoiesis in myelodysplastic syndrome (MDS) progenitors in vitro.2 The elegant experiments by Zhou et al extend their study of TGF-β signaling in MDS and show the constitutive downstream activation of smad2 in MDS bone marrow precursors and its overexpression in MDS-derived CD34+ cells. Suppression of TGF-β activity by shRNA down-regulation of TGF-β receptor I kinase (TBRI) as well as pharmacologic inhibition of TBRI (alk5) by a small-molecule inhibitor (SD-208) leads to a reversal of this TGF-β–mediated inhibition of hematopoiesis in MDS. Furthermore, SD-208 treatment alleviates anemia and stimulates hematopoiesis in vivo in a novel murine model of bone marrow failure generated by the constitutive hepatic expression of TGF-β1. Finally, the enhancement of hematopoiesis seen in several MDS subtypes exposed in vitro to SD-208 underscores the importance of TBRI as a potential therapeutic target in low-risk MDS.

Stem cell apoptosis in MDS, illustrated in the figure, is a facet of the heterogeneity of this disease and the interplay of various mechanisms affecting the marrow microenvironment as well as progenitor proliferation and apoptosis.1 Ineffective hematopoiesis in MDS may be intrinsic to dysregulated gene expression as well as resulting from dysfunctional cell-to-cell contacts within the stromal microenvironment.2,3 TGF-β overactivation in MDS leads to altered stromal cytokine expression with decreased IL-7 and decreased B-cell proliferation4 and enhanced IL-1β and TNFα associated with increased stromal IL-6, IL-8, and IL-32 expression.3 These proinflammatory cytokines are associated with natural killer cell dysfunction5 and may lead to programmed cell death of all hematopoietic cell lineages via autophagy6 or apoptosis.3,7

Our understanding of the molecular pathobiology of MDS and its progression to acute myeloid leukemia (AML) has been made possible by advances in unraveling the molecular underpinnings of acute and chronic leukemias and myeloproliferative syndromes.1 Intrinsic stem and progenitor cell abnormalities in MDS may be attributed to altered DNA methylation and gene silencing. This affects specific hematopoietic lineages, such as Survivin in erythropoiesis and WT-1 and CHK2 during granulopoiesis8, as well as structural genetic alterations.3 While this report does not address the importance of gene silencing and altered differentiation programs in MDS, it nevertheless offers a clear rationale to test compounds such as SD-208 in all phases of MDS. Correlative studies will be needed to determine whether inhibition of TBRI can alter cytokine, chemokine, and oncogene expression profiles in this disease.

Currently approved treatments in MDS are now directed at intermediate and high-risk patients and include immunomodulators, such as lenalidomide and hypomethylating agents 5-azacytidine and decitabine. Patients with low-grade MDS in the future can look forward to these novel hematopoietic enhancing treatment modalities, which provide an alternative to supportive care, transfusions, and growth factors.1 Finally,
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