stimulates granulopoiesis and inhibits apoptosis.

As the authors note, the phenotypic features of C/EBPβ-deficient granulopoiesis resemble those of a myelodysplastic syndrome. Because C/EBPβ mutations and/or dysfunction are known to be involved in the pathogenesis of acute myeloid leukemia (AML), it is possible that inactivation of other C/EBP proteins such as C/EBPβ play a role in myeloid disorders (MDSs) as well. For example, C/EBPβ is frequently inactivated by promoter methylation in AML, and it is possible that C/EBPβ function might be altered in myeloid malignancies and MDSs. Also, the findings by Akagi et al clearly show that a normal white blood cell count in a genetic mouse model can, under steady-state conditions, conceal an important function of the gene in hematopoiesis.

The critical importance of granulopoiesis and granulocyte function in hematology and clinical medicine is obvious, and we have made a lot of progress in deciphering its mechanisms. Nonetheless, tools to more effectively and specifically manipulate granulocyte functions and productions are necessary. The findings presented by Akagi and colleagues might help to design new strategies for overcoming neutropenia and granulocyte dysfunction.

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REFERENCES

Comment on Jasperson et al, page 3257

More ADO about IDO: GVHD

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In this issue of Blood, Jasperson and colleagues show that indoleamine 2,3-dioxygenase (IDO) is a novel component of the inhibition of T-cell activation after allogeneic stem-cell transplantation, and offer a rationale for innovative strategies in the management of GVHD targeting this pathway.

IDO is a key enzyme in tryptophan metabolism that catalyzes the initial rate-limiting step of tryptophan degradation along the kynurenine pathway. Tryptophan starvation by IDO consumption inhibits T-cell activation, while products of tryptophan catabolism, such as kynurenine derivatives and O2 free radicals, regulate T-cell proliferation and survival. Based on these activities, IDO has immunosuppressive function. Accordingly, cell populations, including regulatory dendritic cells, express the functionally active form of IDO, resulting in the suppression of T-cell responses to autoantigens and alloantigens.

Recently, human malignancies including acute myeloid leukemia have been demonstrated to express an active IDO protein, which mediates T-cell tolerance to tumors. 

Graft-versus-host disease (GVHD) is the main cause of morbidity and mortality after allogeneic stem-cell transplantation. In recent years, our knowledge of the pathophysiology of GVHD has increased, but the immunological mechanisms by which GVHD is regulated at both local and systemic levels are still incompletely understood. Jasperson and colleagues have elegantly used an IDO−/− knock-out mouse model to investigate the role of IDO in the context of GVHD. Donor T cells were strictly required to up-regulate IDO expression in gut epithelial cells, and the absence of IDO resulted in increased colon GVHD, which, in turn, shortened survival of IDO−/− mice that had received transplants as compared with wt mice. Interestingly, in IDO−/− mice the major effect is described at the site of GVHD, mainly in the gut, with increased infiltration of proliferating CD4+ and CD8+ T cells, whereas little, if any, systemic effect was found (ie, activation of T cells in lymphoid organs and/or induction of T regulatory cells [Tregs]).

This study reports novel findings that may have significant clinical implications. In particular, the critical role of IDO expression in orchestrating T-cell function during GVHD at the site of inflammation represents a major advance in our knowledge of the environmental effects influencing GVHD tissue injury. Moreover, these results offer a rationale for a novel approach to GVHD management. The modulation of IDO in GVHD target organs may represent an interesting strategy for limiting GVHD by acting at sites where host and donor cells interact, whereas other interventions, such as Treg-infusion therapy, may be used to induce systemic T-cell tolerance within lymphoid organs. However, an effective clinical approach to activate or enhance IDO expression once GVHD has been initiated remains to be elucidated. The preemptive induction of IDO in GVHD target organs before the occurrence of GVHD may have a more relevant clinical impact. However, the lack of IDO expression in other GVHD target tissues, such as liver and skin, indicates that mechanisms other than modulation of tryptophan catabolism may be operative in limiting GVHD in some locations. Future studies addressing these points are warranted.

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