demonstrate that ASK1 is essential for both normal hemostasis and thrombosis. Several reagents targeting MAPK pathways are currently being tested in clinical trials. The enhanced understanding of MAPK signaling pathways in platelets may help direct the evaluation of bleeding as a side effect in clinical trials using these reagents.

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Comment on Shimoji et al, page 1216

GVHD: ferocity affects feracitas

Pavan Reddy  UNIVERSITY OF MICHIGAN

In this issue of Blood, Shimoji et al demonstrate for the first time that female mice that develop acute graft-versus-host disease (GVHD) have reduced fertility and that donor CD8+ T lymphocytes are critical for the destruction of granulosa cells and the eventual loss of ovarian function. Importantly, GVHD prophylaxis preserved fertility in their model.1

For young patients preparing for autologous and allogeneic stem cell transplantation (SCT), infertility is a major concern that has been attributed to myeloablative conditioning, which involves the use of robust systemic regimens such as chemotherapy and total body irradiation. To preserve gonadal function, we are beginning to explore the utility of “reduced-intensity conditioning” regimens.2 Furthermore, fertility preservation requires individualization of treatment of many SCT indications.3 However, although it is well recognized that preparative regimens can cause gonadal failure, the direct effect of GVHD on ovarian function had not been explored until this study.

Symptoms of acute GVHD most frequently present in the skin, gastrointestinal system, and liver. The involvement of other organs such as lung and central nervous system has been posited. In a series of elegant, carefully designed allogeneic murine SCT experiments with female recipients, the authors demonstrate that ovaries are target organs for acute GVHD. They demonstrate a reduction in ovarian size and function that was associated with histopathological features considered to be sine qua non for diagnosis of acute GVHD (infiltration of donor T lymphocytes with target cell apoptosis). They showed that without the use of conditioning (thus eliminating the role of preparative regimens) the degree of acute GVHD severity in their mouse model correlated with decreased ovarian reserve and the impaired ability of allogeneic SCT recipients to get pregnant in mating experiments. Importantly, ovarian functions improved with immune prophylaxis against acute GVHD by tacrolimus and prednisolone. The authors, however, did not explore the effect of GVHD on other organs that could contribute to infertility, namely the hypothalamic-pituitary axis, uterus, or on direct immune rejection of the zygote/embryo. This study primarily used anti-Mullerian hormone (AMH) as a marker for ovarian follicular reserve, and recent work has shown that AMH may directly act on gonadotropin-releasing hormone neurons to disrupt the hypothalamic-pituitary-gonadal axis and fertility.4 These observations are interesting considering previous findings that Leydig cells are targeted in males with acute GVHD,5 and in chronic GVHD males have reduced spermatogenesis.6 Collectively, these data point to the role of both GVHD and conditioning as 2 independent factors in reducing female fertility after allogeneic SCT.

Like novel discoveries, the observations by Shimoji et al are intriguing and thought-provoking. The study raises the possibility of adding gonads as bona fide target organs of acute GVHD. The mechanisms for gonadal GVHD appear to share features related to other target organs, at least as demonstrated by mitigation of ovarian damage by standard immune prophylaxis. However, the specific mechanisms of T-cell infiltration, the key effector pathways, cytokines, and the role of regulatory cells in gonadal GVHD will need to be explored. Clinically, it raises questions and provides potential opportunities to consider for preservation of fertility. Although in humans (where SCTs are almost never performed without preparative regimens), it will be difficult to distinguish the effects of conditioning and treatments of underlying primary disease from acute GVHD. Nevertheless, in light of these new findings, it will be imperative to carry out a more thorough examination of changes that lead to reduced fertility after acute GVHD. Furthermore, a holistic approach to managing fertility will be necessary, as stem cell transplantation has been reported to affect multiple factors that alter it, including chronic GVHD5 and long-term psychological health.8,9 This study demonstrates that the ferocity of acute GVHD affects feracitas and thus raises important...
considerations for the clinicians and patients after allogeneic SCT.

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Pavan Reddy