GLEE-ful for sickle cell pain?

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In this issue of Blood, Vincent et al report on their seminal finding of the contribution of mast cell activation to neurogenic inflammation, and thus to the pathobiology of pain in sickle cell disease (SCD).1

“Painful crises,” or vaso-occlusive episodes, are considered the “hallmark” of SCD and are responsible for >90% of health care encounters in this patient population at an annual hospitalization cost of approximately $1 billion, by 2004 figures.2,3 More than a century after the first description of SCD by Herrick,4 our understanding of pain in this disease is far from complete. However, despite this lack of a thorough understanding, progress has been made in defining the scope of pain. The landmark PISCES study by Smith et al5 established that roughly 30% of SCD patients have daily chronic pain, thus dispelling the long-held view that adult SCD patients have only episodes of pain (the so-called “crises”) interspersed with varying periods of normalcy or “freedom from pain.” Thus, the emerging view of the spectrum of pain in SCD ranges from nociceptive, owing to tissue injury from vaso-occlusion, especially in children and young adults, to increasing frequency of chronic pain, with neuropathic and centralized components in older adults. The lack of a better understanding of the various underpinnings of SCD pain has contributed to stigmatization and disparities in health care.

Vincent et al have conducted a series of elaborate experiments using a sickle cell mouse model (Berkeley mice), and they provide unequivocal evidence about the contribution of mast cell activation to neurogenic inflammation, hyperalgesia, and pain by the elaboration of tryptase, which activates protease activated receptor 2 receptors, as well as by the secretion of substance P and calcitonin gene-related peptide (see figure) as mediators of neurogenic inflammation. As proof of their hypothesis, they clearly demonstrate that inhibitors of mast cell activity by imatinib or stabilization of mast cells by cromolyn sodium leads to a decrease in neurogenic inflammation and results in the reversal of hyperalgesia and the restoration of the analgesic effect of morphine. As a supportive line of experiments, they show that Berkeley SS mice backcrossed with WBB6FM mice, with a point mutation that inactivates c-kit, leads to the generation of Berkeley sickle mice that lack mast cells. These mice behave in a manner similar to control (Hb AA) mice, suggesting an important role of mast cells in neurogenic inflammation and hyperalgesia.

These findings are certainly important contributions to our understanding of the complex mechanisms in SCD pain. In addition, they signal a significant translational potential for treatment of chronic SCD pain by mast cell inactivation or prevention of mast cell degranulation by the repurposing of 2 existing drugs—imatinib and cromolyn sodium, respectively. Of note also is a recently published case report of a patient with SCD in whom chronic myeloid leukemia developed; during treatment with imatinib, the patient remained pain free.6

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REFERENCES
Comment on Stevanović et al, page 1963

**Attack of the T-cell clones**

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In this issue of *Blood*, Stevanović et al demonstrate a possible link between cytomegalovirus (CMV) infection and the induction of CD4-dependent HLA-DP–directed colonic graft-versus-host disease (GVHD).1 Their data suggest that virus-specific T cells mediate this effect via cytokine-induced upregulation of HLA class II molecules, providing further evidence of the plasticity of CD4 T cells in both orchestrating and effecting immune responses, the potential importance of DP matching when choosing a transplant donor, and the possible role of viral infections in providing the inflammatory cues that induce GVHD.

Major histocompatibility complex (MHC) class II proteins (HLA-DR, HLA-DP, and HLA-DQ) play a fundamental role in the regulation of immune responses in the context of recognition by CD4+ T cells. The expression of these transmembrane glycoproteins is largely restricted to thymic epithelial cells and to cells specialized in the capture and presentation of extracellular antigens, such as B cells, cells of monocyte-macrophage lineage, and dendritic cells. There are 2 general cell-type–specific modes of MHC-II expression: constitutive and inducible. Both constitutive and inducible MHC-II expression can be modulated in a cell-type–specific manner by various secondary stimuli. Constitutive expression is mainly restricted to thymic epithelial cells and antigen-presenting cells. Other types of cells do not usually express MHC-II molecules, although they can often be induced to express them after exposure to interferon gamma and other cytokines, dependent on the status of class II trans-activator protein, a coactivator of the MHC-II gene promoter. Therefore, inflammatory cues may be important in promoting the direct activation of CD4+ T cells, as well as being indirectly relevant in influencing the activation status of antigen-presenting cells.

The complex relationships that exist between CMV infection and clinical outcomes after allogeneic transplantation have been recognized for some time.2,3 The observation that increased immune compromise resulting both from the process and the treatment of GVHD results in an increased propensity to CMV infection is intuitively understandable. The converse, that CMV serostatus or infection correlates with an increased incidence of GVHD, is also well recognized, although the mechanistic explanation has remained less clear.3,4 The study by Stevanović et al provides one possible mechanism linking these prior observations (see figure). Their findings suggest that CMV-reactive T cells can directly induce upregulation of MHC-II molecules on tissues via the release of inflammatory cytokines, and that these tissues then become targets for alloreactive T-cell clones. Furthermore, they demonstrate that in the setting of persistent mixed T-cell chimerism, as more commonly occurs after reduced intensity and T-cell–depleted transplantation, recipient-derived virus-specific T cells may themselves upregulate MHC-II molecules after recognition of a cognate antigen, which can in itself act as a trigger for allorecognition by class II-mismatched CD4+ T cells. Elimination of the recipient T cells and a switch to full-donor chimerism might further fuel the process by eradicating CMV–specific T-cell immunity, allowing further uncontrolled proliferation of CMV, particularly in the context of CMV-seronegative donors or enhanced immune suppression given to treat GVHD.

What are the implications of these findings? Could this be part of the explanation for the failure of reduced intensity-conditioning regimens to deliver the expected decrease in the incidence of GVHD despite a reduction in conditioning-related inflammation? Should we be considering evaluation of viral suppression at the time of DP-mismatched donor lymphocyte infusions (DLIs)? It is notable that the 2 patients outlined in this study underwent T-cell–depleted transplantation and received prophylactic CD8-depleted DLIs at early time points after transplantation, when CMV reactivation is more commonly detected. Therefore, questions arise about the broader relevance of the findings in the contexts of unrelated donor allogeneic transplantation, DLIs delivered at later time points, and full-donor chimeras. Certainly, the findings lead to a number of testable hypotheses. Although there is no a priori reason to suspect that other viruses, such as norovirus, could not have a similar impact, at least in the more direct influence of upregulation of MHC-II molecules on target tissues within the gut, the numerical preponderance of CMV makes it feasible to consider epidemiological analyses aimed at determining whether the excess GVHD incidence noted in DP-mismatched transplant cohorts correlates with recipient CMV serostatus or, perhaps more importantly, CMV reactivation. These trends may help to show whether the findings are broadly relevant to donor choice and events earlier posttransplantation, when inflammation secondary to transplant conditioning may override any influence of cytokines released by virus-specific T cells. Stratification for conditioning intensity and T-cell depletion would clearly be important in any correlative epidemiological studies. Because other factors clearly drive GVHD incidence, the background noise in the system may act to obscure any true influence of DP mismatching and CMV infection, requiring careful interrogation of large-registry data sets. If these findings do have broader relevance, do they help us to choose an...
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