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CLINICAL TRIALS AND OBSERVATIONS

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CD24Fc to DAMPen GVHD

Paul J. Martin | Fred Hutchinson Cancer Center and University of Washington

Agents historically used to prevent graft-versus-host disease (GVHD) after allogeneic hematopoietic cell transplant (HCT) have typically targeted T cells. In this issue of *Blood*, Magenau et al[1] show that agents targeting antigen-presenting cells can also help prevent GVHD.

The success of allogeneic HCT for treatment of neoplastic diseases requires careful balancing between interacting processes. Intensive treatment with chemotherapy and radiotherapy before HCT decreases the burden of malignant cells in the recipient but also causes tissue damage. Donor T cells deplete viable malignant cells that persist after HCT but also cause GVHD, which is worsened by tissue damage. Immunosuppressive treatment after HCT controls GVHD but increases the risk of infections.

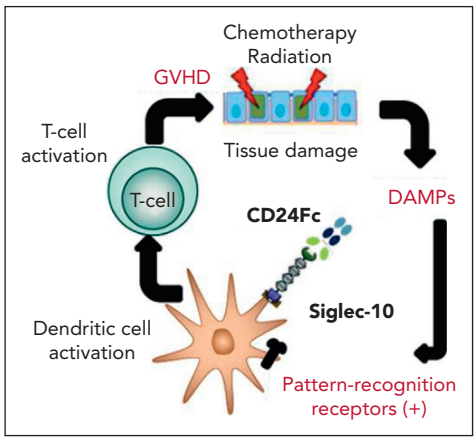
GVHD involves both adaptive responses mediated by donor T cells and innate immune responses mediated by other cell types, including dendritic cells (DCs) that present recipient alloantigens.[2] Dendritic cells have a wide variety of receptors that recognize pathogen-associated molecular patterns (PAMPs) not present in host tissues (ie, infectious nonself) and damage-associated molecular patterns (DAMPs) (ie, noninfectious self) (see figure).[3] Binding of PAMPs and DAMPs to toll-like receptors stimulates DCs through myeloid differentiation primary response 88 and nuclear factor-κ light chain enhancer of activated B cells (NF-κB) signaling, thereby enhancing their ability to present antigens to T cells.[4]

PAMP and DAMP signaling differ in 1 critical respect. DAMPs, such as high-mobility group box 1 and heat shock proteins 70 and 90, bind to CD24, whereas PAMPs do not.[5] In turn, CD24 binds to sialic acid–binding immunoglobulin-type lectin 10 (Siglec-10; homolog of Siglec-G in mice), which has an intracellular domain that inhibits NF-κB signaling. CD24 thereby regulates DAMP-mediated signaling while leaving PAMP-mediated signaling and pathogen defenses intact.

Preclinical studies showed that GVHD is worsened by the absence of Siglec-G in recipient hematopoietic cells and by the absence of CD24 in donor T cells.[6] Further experiments showed that administration of a CD24Fc fusion protein ameliorated GVHD through its effects on recipient antigen-presenting cells. It was later discovered that Siglec-G–CD24 interaction regulates DAMP-mediated responses not only in DCs but also in T cells, raising concerns that a decrease in T-cell–mediated graft-versus-leukemia activity could offset the benefits of controlling GVHD with a CD24Fc fusion protein. Toubai et al[7] addressed this concern by showing that administration of a CD24Fc fusion protein ameliorated GVHD while preserving sufficient graft-versus-tumor activity in murine models, thereby setting the stage for clinical translation of these important preclinical findings.

The clinical trial reported by Magenau et al involved a double-blind, placebo-controlled dose-finding and treatment duration phase that evaluated groups of 6 patients, followed by an open-label expansion phase that enrolled 20 additional patients treated with the regimen recommended from results of dose-escalation phase. All patients had human leukocyte antigen–matched unrelated donors and received myeloablative conditioning regimens and standard post-transplant immunosuppression with tacrolimus and methotrexate.

The primary end point was moderate to severe grade 3 to 4 acute GVHD-free survival at 180 days after HCT. The



Pretransplant chemotherapy and irradiation release damage-associated molecular patterns (DAMPs) that bind to pattern-recognition receptors and activate dendritic cells to present antigen to donor T cells, thereby worsening graft-versus-host disease (GVHD). Binding of CD24Fc with sialic acid–binding immunoglobulin-type lectin 10 (Siglec-10) inhibits pattern-recognition receptor signaling and the downstream effects of DAMPs on dendritic cell activation, T-cell activation, and GVHD. Figure adapted from the visual abstract of the article by Magenau et al.[1]

Kaplan-Meier estimate for the group of 26 patients treated with the recommended phase 2 dose was 96%, compared with 74% for a group of 92 propensity-matched historical controls from the Center for International Blood and Marrow Transplant Research database. Further analysis showed no evidence of statistically or clinically significant differences in overall survival or the risks of chronic GVHD or relapse between the 2 groups. These important results stand as the first proof of concept that targeting DAMP signaling could dampen acute GVHD in humans.

The authors appropriately note the statistical limitations of the small sample size and the use of historical controls. They also call attention to the need for further studies to evaluate whether comparable results could be achieved with less than the 3-dose regimen of CD24Fc used in the expansion phase of the current study. Two participants developed Stevens-Johnson syndrome. Whether this rare complication was related to administration of CD24Fc cannot be excluded and will require careful monitoring and evaluation in future trials.

From a basic science perspective, the studies with CD24Fc suggest that the Siglec-10/Siglec-G pathway inhibits signaling from a wide variety of DAMPs or from a subset of DAMPs that are particularly involved in GVHD. Binding between CD24 and Siglec-10/Siglec-G can occur without the overt presence of DAMPs (see Figure 3 in the study by Chen et al[5]). Further studies will be needed to elucidate the extent to which DAMP binding with CD24 enhances CD24 binding with Siglec-10/Siglec-G, to define the spectrum of DAMPs that bind with CD24, and to unravel the molecular basis of the specificity of CD24 for multiple DAMPs.

From a clinical perspective, results of the current study signal the merit of further development to evaluate the extent to which ancillary targeting of DAMP signaling with CD24Fc could be used together with conventional immunosuppression to prevent acute GVHD without increasing the risks of recurrent or progressive malignancy or infection, especially in patients treated with high-intensity regimens of chemotherapy and radiation before HCT. Of further interest, recent studies have suggested that CD24Fc could also have a therapeutic role in a wide variety of other inflammatory conditions associated with tissue damage.[8]

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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HEMATOPOIESIS AND STEM CELLS

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EBV-infected hematopoietic stem cells drive CAEBV

Rajiv Khanna[1] and Maher K. Gandhi[2,3] | [1]QIMR Berghofer Medical Research Institute; [2]University of Queensland; and [3]Princess Alexandra Hospital

In this issue of *Blood*, Wang et al[1] report on their use of a combination of molecular technologies including quantitative polymerase chain reaction (qPCR), PrimeFlow RNA assay, and single-cell RNA-sequencing (scRNA-seq) to delineate the critical role hematopoietic stem cells (HSCs) infected with Epsetein-Barr virus (EBV) in the origin of chronic active EBV (CAEBV) disease. These findings will have major implications for understanding the disease pathogenesis of and developing novel therapeutic strategies for CAEBV disease.

Acquisition of EBV infection frequently occurs soon after birth with minimal clinical consequences, but the infection leads to establishment of a pool of latently infected B cells, kept under strict control by virus-specific $CD8^+$ and $CD4^+$ T cells.[2] However, primary EBV infection in young adolescents can lead to severe clinical symptoms with uncontrolled proliferation of $CD8^+$ T cells, which are predominantly directed at EBV-encoded lytic antigens.[3] Infrequently, this primary EBV infection can lead to nonresolving chronic viral reactivation, also referred to as CAEBV disease.[4] In some individuals, prolonged CAEBV disease can lead to a series of fatal complications including gastrointestinal ulceration, hepatic failure, and hemophagocytic lymphohistiocytosis (HLH).[5]

The management of systemic CAEBV disease is very challenging. "Cooling" therapy incorporating steroids, cyclosporine, and etoposide is typically given, and this is frequently followed by combination chemotherapy such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) or ESCAP (etoposide, cytarabine, l-asparaginase, methylprednisolone, and prednisolone).[6] Although responses are common, they are frequently only partial or transient and should be seen as a bridge to what currently remains the only curative option, that is, allogeneic