with FXII ASO for 2 months. This treatment paradigm reduced cerebral inflammation and fibrin deposition but, importantly, also decreased neuronal damage and improved cognitive performance in the Barnes maze and contextual fear-conditioning paradigm. These results underline the strong links that exist among the coagulation cascade, neuroinflammation, and neuronal damage (see figure).[3] Nevertheless, the nature of the fibrin deposits found in this study (ie, whether they are intravascular clots, perivascular deposits, and/or actual parenchymal deposits associated with Aβ) cannot be evaluated from the data. Future studies are also warranted to determine the exact temporal effects of FXII and the downstream members of the coagulation cascade on the specific components of the neuronal circuitry.

Given that FXII binds to endothelial cells via the gC1q receptor, could FXII extravasate into the brain and bind to central nervous system (CNS) proteins?[9] Do the different Aβ species in the brain activate FXII to a different extent than those in the circulation? These are some pertinent questions raised by the exciting findings of this study. As the authors suggest, activation of FXII ultimately leads to release of bradykinin, which may increase blood–brain barrier permeability. Therefore, entry of FXII into the CNS, similar to that which is well established for fibrinogen, is likely. Determining the presence and fate of FXII in the CNS may thus reveal unexpected and highly interesting novel binding interactions between FXII and CNS proteins. As for the latter question, the group previously showed in vitro that oligomeric $A\beta_{42}$ in plasma activates FXII more potently than that observed for its monomeric and fibrillar forms.[7] However, it is not known how the aggregation state of $A\beta_{42}$ and possibly of other Aβ species determines the activation of FXII in vivo, especially in the critical brain milieu.

This exciting study by Chen and colleagues positions FXII among the key players of the coagulation cascade that contribute to AD pathogenesis by instigating neuroinflammatory responses. It shows encouraging promise for FXII and other members of the coagulation cascade as potential, highly needed novel therapeutic targets in neurodegenerative diseases.

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TRANSPLANTATION

Comment on Du et al, page 2570

Pirfenidone: a breath of fresh air for cGVHD

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In this issue of *Blood*, Du et al[1] show that pirfenidone has remarkable therapeutic efficacy in bronchiolitis obliterans (BO) models of chronic graft-versus-host disease (cGVHD). Their data support the use of pirfenidone as a new agent in early-phase clinical trials for cGVHD treatment.

cGVHD is a frequent and lethal complication arising in patients that receive allogeneic hematopoietic stem cell transplants (HSCTs). Earlier it was widely thought that graft-versus-host disease (GVHD) that presented within 100 days posttransplant was acute GVHD (aGVHD), whereas GVHD that arose past the "100-day" mark was cGVHD. This arbitrary cutoff is now accepted to be an oversimplification, with the knowledge that symptoms of cGVHD can overlap and coexist in time with aGVHD. A number of studies in the recent past have shown that cGVHD is initiated by T cells, predominantly the T-helper 17 (Th17)/IL-17–secreting CD8+ T (Tc17) cells with involvement of the follicular T-helper cells that foster aberrant and elevated germinal center reactions ultimately promoting both allo- and auto-antibody production.[2]

Clinically, cGVHD is characterized mainly by scleroderma, BO, and oral lichen planus–like lesions.[2-4] There is significant morbidity and mortality associated with cGVHD; in particular, patients with BO have a 5-year mortality rate of 41%. These poor results underscore the need to develop effective anti-cGVHD therapies.[5]

Pirfenidone is an oral antifibrotic therapy that was recently approved by the US Food and Drug Administration for the treatment of idiopathic pulmonary fibrosis, where it has been shown that pirfenidone reduces disease progression and increases lung function in humans.[6] Several publications have also shown the protective effect of pirfenidone in murine lung allotransplant/pulmonary fibrosis models.[7] Given these complementary findings, it makes perfect sense to investigate whether pirfenidone would have any therapeutic benefit

in cGVHD, particularly in models where BO is the defining cGVHD symptom.

In the first part of the paper, the authors employ the elegant B6 into B10.BR model of cGVHD that recapitulates human BO syndrome, and demonstrate that therapeutic administration of pirfenidone reverses lung fibrosis. Mechanistically, the authors show that alternatively activated M2 macrophages are predominant drivers of lung fibrosis and that pirfenidone significantly reduces M2 macrophage infiltration into the lungs as well as M2 macrophage-mediated transforming growth factor-β (TGF-β) production. Pirfenidone treatment also results in reduced germinal center B cells and T-follicular helper cell frequencies, an important mediator of auto/alloantibody–driven pathologies. The authors also show that pirfenidone administration at a later stage of disease is still very effective at reducing BO. This novel finding is extremely important for 2 reasons: (1) there is an option of administering pirfenidone intermittently for patients who cannot tolerate continuous dosing without compromising drug efficacy and (2) the timing of TGF-β inhibition. TGF-β is an important regulatory cytokine, and neutralizing TGF-β early posttransplant may have deleterious consequences by promoting cellular cytotoxicity, whereas TGF-β that is produced late after HSCTs has been shown to drive cGVHD.[8] Therefore, it is tempting to speculate that the "late" timing of TGF-β inhibition by pirfenidone may not result in an inadvertent proliferation of alloreactive donor T cells nor affect the regulatory T-cell subset, a hypothesis that must be tested.

In the second part of the paper, Du et al move to evaluate the therapeutic potential of pirfenidone in 2 independent sclerodermatous models of cGVHD. Here, the authors observe that despite reduction in cutaneous macrophage infiltration due to pirfenidone administration, there was no overall clinical benefit. One pertinent area of investigation is the effect of pirfenidone on the Th17/Tc17 subset of cells, since the authors show that pirfenidone has variable efficacy in the sclerodermatous models of cGVHD in which Th17/Tc17 cells play an important role. Another area of examination is the effect of pirfenidone on the beneficial effects of graft-versus-leukemia.

A major roadblock in developing new therapeutics for cGVHD has been the lack of well-established preclinical mouse models that can effectively recapitulate the diverse pathology of cGVHD as seen in humans. In this paper, Du et al effectively employ 3 different mouse models of cGVHD to evaluate the therapeutic potential of pirfenidone and show particular promise in the case of BO-dominant cGVHD pathology.

Overall, the data presented in this paper support the evaluation of oral pirfenidone in phase 1 clinical trials for cGVHD-BO patients.

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