Uncovering a mechanism causing chronic graft-vs-host disease after bone marrow transplant

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Allogeneic bone marrow transplant (BMT) is an essential treatment to cure patients with blood cancers such as leukemia. In patients who have undergone chemotherapy and radiation, a small number of cancer cells can remain in the bloodstream and allow the malignancy to recur.

Replacing host bone marrow is the best strategy for preventing relapse but recipients cannot always find an ideal, biologically matched donor. The less well-matched the donor, the higher the risk for developing graft-versus-host disease (GVHD). In GVHD, donor cells trigger an immune response that attacks normal tissues, leading to a chain reaction of cellular and molecular responses that increase morbidity and mortality in these patients. A long-standing question has been how to improve the success of BMT by reducing GVHD incidence while, at the same time, preserving the anti-tumor response of donor cells.

New research by a team of investigators at the Medical University of South Carolina (MUSC) directed by Xue-Zhong Yu, M.D., professor of Microbiology and Immunology, in collaboration with researchers at the University of Minnesota, demonstrates that one particular family of microRNAs (miRs), called miR-17-92, is responsible for the T-cell and B-cell pathogenicity that causes GVHD. The findings were reported in an article prepublished online on March 12, 2018 by *Blood*.

GVHD can be divided into acute (aGVDH) or chronic forms (cGVHD). "They are very different diseases," explains Yongxia Wu, Ph.D., a postdoctoral fellow and lead author on the article. "Our ability to prevent or treat aGVHD has considerably improved, but the incidence of cGVHD continues to increase. Chronic GVHD has a different pathophysiology and different target organs than aGVHD. It's been a big challenge to try to find a target for cGVHD therapies, because of the more complex immune reaction in cGVHD and the fact that its cellular and molecular mechanisms are not as well understood."

Chronic GVHD is characterized by autoimmune-like, fibrotic changes in multiple organs such as the skin (causing scleroderma) and the lungs (causing bronchiolitis obliterans), and fibrosis of the salivary glands, liver, and gut. With 30 to 70 percent of patients who receive allogeneic BMT developing cGVHD, the lack of effective therapies is a major unmet clinical need.

The MUSC team previously found that, in aGVHD, miR-17-92 played a critical role in regulating CD4 T-cell proliferation and Th1 and Treg differentiation. Based on this work, they decided to investigate whether miR-17-92 regulates T- and B-cell differentiation and function in the development of cGVHD.

"We decided to extend our aGVHD study to cGVHD. But there's no single, well-defined murine model that can reflect all of the clinical manifestations seen in cGVHD patients," explains Wu. "Different patients experience different symptoms because cGVHD can be manifested in many organs—some patients have skin symptoms, some have lung symptoms—it varies. So, we decided to study four different cGVHD models to best understand how miR-17-92 contributes overall, across many clinical presentations."

The team undertook a series of experiments to define the role of miR-17-92 in regulating T- and B-cell pathogenicity using murine models of allogeneic BMT, including models of scleroderma that had transitioned from aGVHD to cGVHD, classic cGVHD scleroderma, lung inflammation and

a lupus-like condition. The team also conducted two clinical translation studies to test whether pharmacologically blocking miR-17-92 might have clinical relevance in the lupus-like condition and the scleroderma cGVHD model.

Their results demonstrated shared mechanisms by which miR-17-92 mediates cGVHD progression—namely by regulating T helper-cell differentiation, B-cell activation, germinal center responses, and autoantibody production. The clinical translation studies also found that miR-17 blockade alleviated proteinuria (in the lupus-like condition) and scleroderma symptoms.

"The mechanism for how miR-17-92 regulates T- and B-cells was very consistent. In other words, we did not find any big differences among the models," says Wu. "So, we not only found a new mechanism for cGVHD development by demonstrating that this miR-17-92 is heavily involved in the T- and B-cell responses that lead to cGVHD, but we also found that blocking miR-17 substantially reduced cGVHD symptoms in mice. That's exciting because it provides strong evidence that this miR may be a good target for controlling cGVHD after allogeneic BMT."

Although miR-17-92 has been well studied, its role in cGVHD development has never before been defined. Because cGVHD has a similar pathophysiology to some autoimmune diseases, it is likely that these findings will be useful for developing new treatments and preventive therapies in other conditions.

"We are very excited to publish this work because we are hoping that a clinical research group will be inspired to take our study findings further in patients," says Wu.

In the meantime, the MUSC team, led by Yu, will continue their work and try to extend the current findings by investigating how other miRs may be involved in regulating T- and B-cell function during allogeneic BMT.

More information: Yongxia Wu et al, MicroRNA-17-92 is required for T-cell and B-cell pathogenicity in chronic graft-versus-host disease in mice, *Blood* (2018). DOI: 10.1182/blood-2017-06-789321

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