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Protein's role in lupus development

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Northwestern Medicine scientists have demonstrated that the loss of a protein called Bim in macrophages—a type of immune cell—leads to the development of lupus-like disease in mice. The findings, published in the *Journal of Experimental Medicine*, suggest that Bim may be a novel therapeutic target for lupus in humans.

Harris Perlman, PhD, chief of Rheumatology in the Department of Medicine, and Carla M. Cuda, PhD, research assistant professor of Medicine in the Division of Rheumatology, were co-senior authors of the study.

"Our study is the first to suggest an essential role for Bim in monocytes and macrophages in the development of lupus-like disease in mice," Perlman said. "The idea now is to parlay that into patient material."

Systemic lupus erythematosus, commonly called lupus, is a chronic inflammatory disorder in which the immune system mistakenly attacks its own healthy tissue, including internal organs. The cause of lupus is unknown.

A prevailing theory is that the systemic autoimmunity seen in lupus is induced by abnormalities in apoptosis—the process of programmed cell death—as well as in the clearance of these apoptotic cells.

The protein Bim, which is expressed in immune cells, is highly involved in the cell death pathway. Previous studies have demonstrated that mice lacking the gene for Bim develop a lupus-like disease within 12 months.

But it was unclear which type of immune cell was most important to the development of lupus.

"The original dogma suggested that it's your lymphocytes—your T- and B-cells," explained Perlman, also the Mabel Greene Myers Professor of Medicine. "But therapies that have tried to target T- and B-cells cells have all failed. So, we suggested maybe it's something else."

In the current study, the scientists investigated inactivating Bim in a different population: macrophages and their precursors, monocytes. Macrophages are a type of immune cell in tissue that recognize and digest target cells, as well as produce inflammatory cytokines.

The scientists discovered that when the Bim gene was removed in monocytes and macrophages, the mice developed a lupus-like disease—unlike when the same gene was knocked out in T- or B-cells.

The findings suggest for the first time that Bim may be involved in a non-cell death pathway, and may play a role in controlling macrophage function—which could be targeted for novel treatments.

The study also identified a gene signature indicative of lupus in kidney macrophages of mice. In future research, the team intends to investigate this same signature in humans. "The goal is to then determine if we can discover novel therapeutics that might be important for treating these patients," said Perlman, also a member of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University.

Among other future research directions, the team is also investigating if the same system is involved in neuropsychiatric lupus, a major comorbidity. "Lupus is extremely heterogeneous in terms of how many systems are affected and what symptoms patients present with," Cuda explained. "So a major next step is to see how many other types of

disease manifestations we can utilize this model for, in terms of understanding the impact of macrophage-specific Bim."

More information: FuNien Tsai et al. Bim suppresses the development of SLE by limiting myeloid inflammatory responses, *Journal of Experimental Medicine* (2017). DOI: 10.1084/jem.20170479