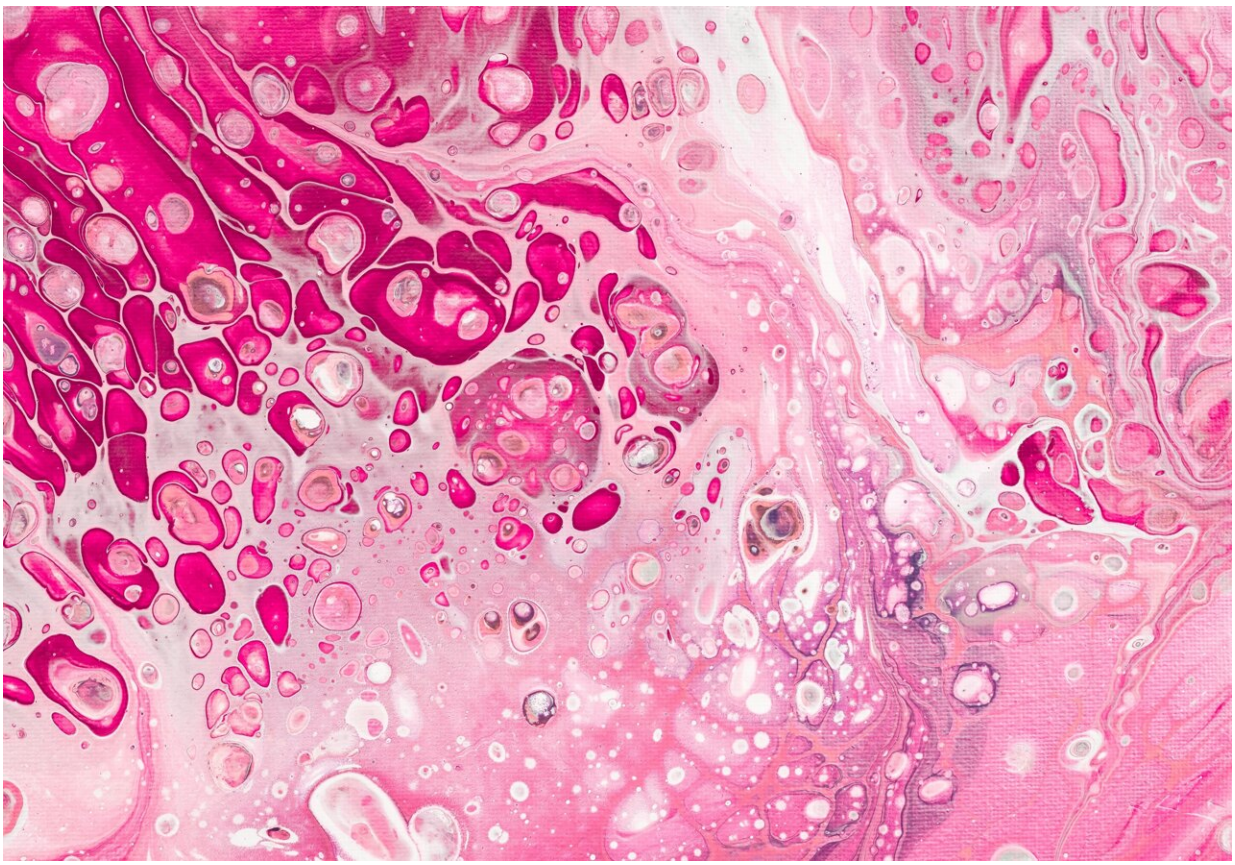
Medical Xpress

Researchers discover that blocking ephrin B2 signaling can stop multiple myeloma growth

February 7 2024



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Cedars-Sinai Cancer investigators have discovered a protein expressed on multiple myeloma cancer cells that drives disease growth and development. The new study found that blocking part of the protein's

unique signaling pathway stops myeloma growth in culture and in laboratory mice. Their study was published in the journal *Cancer Research*.

The protein studied, called ephrin B2, is a powerful new target in the treatment of patients with multiple myeloma, a disease that has numerous partially effective treatments, but no cure. Based on these findings, investigators are now working on the development of therapies to target this protein in patients.

Myeloma cells grow inside a patient's bone marrow. Unlike many types of cancer cells, multiple myeloma cells cannot live outside the patient, meaning they rely on signals from the patient's healthy cells in order to grow. Investigators sought to determine the source of that signal as a potential way to block myeloma cells' growth.

The investigators discovered that endothelial cells, which line blood vessels, express unique receptors called Eph receptors. These Eph receptors bind with ephrin proteins expressed by myeloma cancer cells, triggering growth of the myeloma cells. Most interestingly, the "forward signal" from the myeloma cell (expressing ephrin) to the endothelial cell (expressing Eph receptor) does not significantly affect myeloma growth; however, the "reverse signal" from the endothelial cell to the myeloma cell drives the cancer.

Investigators cultured human myeloma cancer cells along with many different types of blood vessel cells. They compared the genes expressed by the blood vessel cells that spurred cancer growth with the genes expressed by the blood vessel cells that did not spur growth. Through a process of elimination, they were able to identify the unique role of ephrin B2 in multiple myeloma.

"We showed that if we block the reverse signal of ephrin B2, a member

of the ephrin family of proteins expressed on myeloma cells, the myeloma cells could not grow in vitro or in vivo in laboratory mice, a striking effect," said hematologist-oncologist Joshua Sasine, MD, Ph.D., assistant professor of Medicine at Cedars-Sinai and first author of the study. "This is the first study to identify this pathway in multiple myeloma, and the effect of inhibiting ephrin B2 on inhibiting myeloma cancer growth, suggesting a great therapeutic target for treating patients."

"Multiple myeloma is incurable, and fundamental biological insights remain lacking in this disease," said John Chute, MD, director of the Division of Hematology and Cellular Therapy at Cedars-Sinai Cancer and senior author of the study. "Our evidence suggests the importance of the reverse signaling pathway of ephrin B2 in regulating multiple myeloma development and progression, and that inhibiting this signal in a targeted way abolishes multiple myeloma growth."

Corresponding clinical data suggests that ephrin B2 expression correlates with poor outcomes in multiple myeloma patients. Given the substantial progress that has been made in the development of therapeutics to target these proteins, the ephrin B2 reverse signaling pathway represents a novel therapeutic target for this intractable cancer.

More information: Joshua P. Sasine et al, Inhibition of Ephrin B2 Reverse Signaling Suppresses Multiple Myeloma Pathogenesis, *Cancer Research* (2024). DOI: 10.1158/0008-5472.CAN-23-1950

Provided by Cedars-Sinai Medical Center