

Key bone marrow protein identified as potential new leukemia treatment target

April 15 2013

A new study on how the progression of acute lymphocytic leukemia (ALL) is influenced by the bone marrow environment has demonstrated for the first time that targeting a specialized protein known as osteopontin (OPN) may be an effective strategy to increase the efficacy of chemotherapy in patients with this type of blood cancer. Study data were published online today in *Blood*, the Journal of the American Society of Hematology (ASH).

[Acute lymphocytic leukemia](#) (ALL) is a cancer of white blood cells, which normally fight infection in the body. ALL develops when abnormal [white blood cells](#) grow quickly but do not properly develop, crowding out normal cells and inhibiting healthy function. While patients with ALL typically experience good initial responses to treatment with chemotherapy, many suffer relapses and their disease becomes extremely difficult to treat (refractory) when a small percentage of [abnormal cells](#) reemerge after having evaded the effects of the cytotoxic drug. Relapsed disease arises from residual [malignant cells](#) below the level of detection at the time the patient has his or her initial response (a condition known as [minimal residual disease](#) or MRD).

[Treatment strategies](#) aimed at combating chemotherapy resistance and reducing MRD may have the potential to increase overall survival.

Previous studies have demonstrated that, even when MRD is not completely eradicated, a reduction in MRD burden correlates with significantly higher overall survival. One proposed approach to

improving chemotherapy efficacy and reducing MRD includes identifying lingering, dormant [leukemic cells](#) and forcing them into active cell division to make them responsive to treatment, since chemotherapy targets cells that are rapidly dividing.

"Previous studies have suggested that osteopontin (OPN), a protein present in the bone marrow, may regulate the way [tumor cells](#) grow and spread throughout the body; however, its specific role in the progression of leukemia has not been well studied," said study author Dorothy Sipkins, MD, PhD, of the Section of [Hematology/Oncology](#) at the University of Chicago. "Our research aimed to understand the interactions of OPN and leukemic cells in specific areas of the bone marrow, known as niches, which may allow the cells to 'hide' in the dormant state and evade the effects of chemotherapy."

To better understand the interactions of the leukemic cells and OPN within these bone marrow niches and whether leukemic cells can hide, remain dormant, and evade chemotherapy, Dr. Sipkins and colleagues conducted a series of analyses and experiments in mouse models. They further evaluated how controlling the expression of OPN would affect the activity of the leukemic cells and how that control may better sensitize the leukemic cells to the effects of chemotherapy.

Dr. Sipkins' team found that inhibiting the interaction of the OPN with leukemic cells in the bone marrow niches led the dormant cells to actively proliferate, which allows the chemotherapy to identify and target them. When OPN was blocked using neutralizing antibodies and then followed by chemotherapy treatment, leukemic cells responded to the chemotherapy and overall MRD was significantly reduced. These data suggest that OPN may serve as an anchor for leukemic cells within areas of the bone marrow that allow the cells to remain dormant, encouraging them to localize to these areas.

"After examining the interactions between the leukemic cells, OPN, and the bone marrow microenvironment, we learned that the bone marrow environment can promote leukemia cell dormancy, creating a form of resistance to chemotherapy. This is an important target, because if we can disrupt the interaction between the OPN and the leukemic cells, we may be able to make this disease more responsive to [chemotherapy](#)," said Dr. Sipkins. "We've traditionally designed therapies that focus solely on the cancer cells, but future strategies for ALL and other [blood cancer](#) treatment may be enhanced by targeting not just the cancer cells but the environment with which the cells interact."

Dr. Sipkins and her team further suggest that in order to develop a leukemia treatment that neutralizes OPN, studies would need to assess the potential toxic side effects on normal stem cells that cohabit the [bone marrow](#) microenvironment.

Alternatively, a therapy could be developed to reinforce the interaction between OPN and leukemia cells, which would help maintain the dormant state in an effort to prevent or slow disease progression.

Provided by American Society of Hematology

Citation: Key bone marrow protein identified as potential new leukemia treatment target (2013, April 15) retrieved 4 May 2024 from <https://medicalxpress.com/news/2013-04-key-bone-marrow-protein-potential.html>

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