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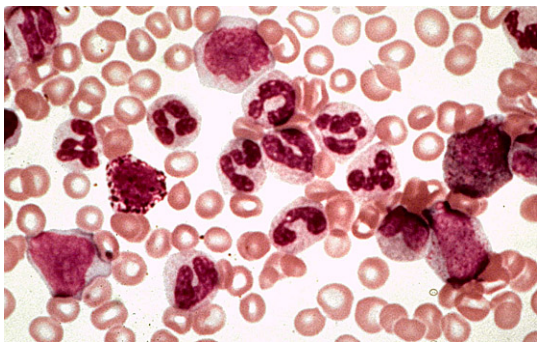
Enzyme Accelerates Malignant Stem Cell Cloning in Chronic Myeloid Leukemia

An international team, headed by researchers at the University of California, San Diego School of Medicine, has identified a key enzyme in the reprogramming process that promotes malignant stem cell cloning and the growth of chronic myeloid leukemia (CML), a cancer of the blood and marrow that experts say is increasing in prevalence.



Chronic myeloid leukemia blood cells.

The findings are published in the Dec. 24 online early edition of the *Proceedings of the National Academy of Sciences* (*PNAS*).

Despite the emergence of new therapies, such as tyrosine kinase inhibitors, CML and other leukemias remain problematic because some cancer stem cells avoid destruction and eventually regenerate themselves, a stem cell process known as self-renewal that can result in a return and spread (metastasis) of the disease.

In the PNAS paper, principal investigator Catriona H. M. Jamieson, MD, PhD, associate professor of medicine at UC San Diego, with colleagues in the United States, Canada and Italy, report that inflammation – long associated with the development of cancer – boosts activity of an enzyme called adenosine deaminase or ADAR1.

Expressed during embryogenesis to help blood cell development, ADAR1 subsequently turns off and is triggered by viral infections where it protects normal hematopoietic stem cells from attack. In leukemia stem cells, however, overexpression of ADAR1 enhances the missplicing of RNA, which leads to greater self-renewal and therapeutic resistance of malignant stem cells.

The findings build upon previous studies by Jamieson and others that elucidate the effects of RNA missplicing and instability. “People normally think about DNA instability in cancer, but in this case, it’s how the RNA is edited by enzymes that really matters in terms of cancer stem cell

generation and resistance to conventional therapy."

The described RNA editing process, which occurs in the context of human and other primate specific sequences, also underscores the importance of addressing inflammation as "an essential driver of cancer relapse and therapeutic resistance," Jamieson said. It also presents a new target for future therapies.

"ADAR1 is an enzyme that we may be able to specifically target with a small molecule inhibitor, an approach we have already used effectively with other inhibitors," said Jamieson. "If we can block the capacity of leukemia stem cells to use ADAR1, if we can knock down that pathway, maybe we can put stem cells back on the right track and stop malignant cloning."

CML is a cancer initiated by a mutant gene called BCR-ABL in blood forming stem cells that leads to an expansion of white blood cells and their precursors. It is typically slow-growing and often not diagnosed until its later stages when there can be a sudden, dramatic increase in malignant cells, known as blast crisis. Median age of diagnosis is 66 years; incidence of the disease increases with age. Despite tremendous advances in BCR-ABL tyrosine kinase inhibitor therapies, the majority of patients relapse if therapy is discontinued, in part as a result of dormant cancer stem cell resistance. This work suggests a novel mechanism for overcoming cancer stem cell resistance to therapy that may prevent relapse and progression.

The estimated prevalence of CML in the United States is 70,000 persons with the disease, projected to steadily increase to approximately 181,000 by 2050. CML is initiated by the mutant BCR-ABL gene, but scientists have not yet identified the cause of the mutation.

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