In multiple myeloma, high levels of enzyme ADAR1 are associated with reduced survival

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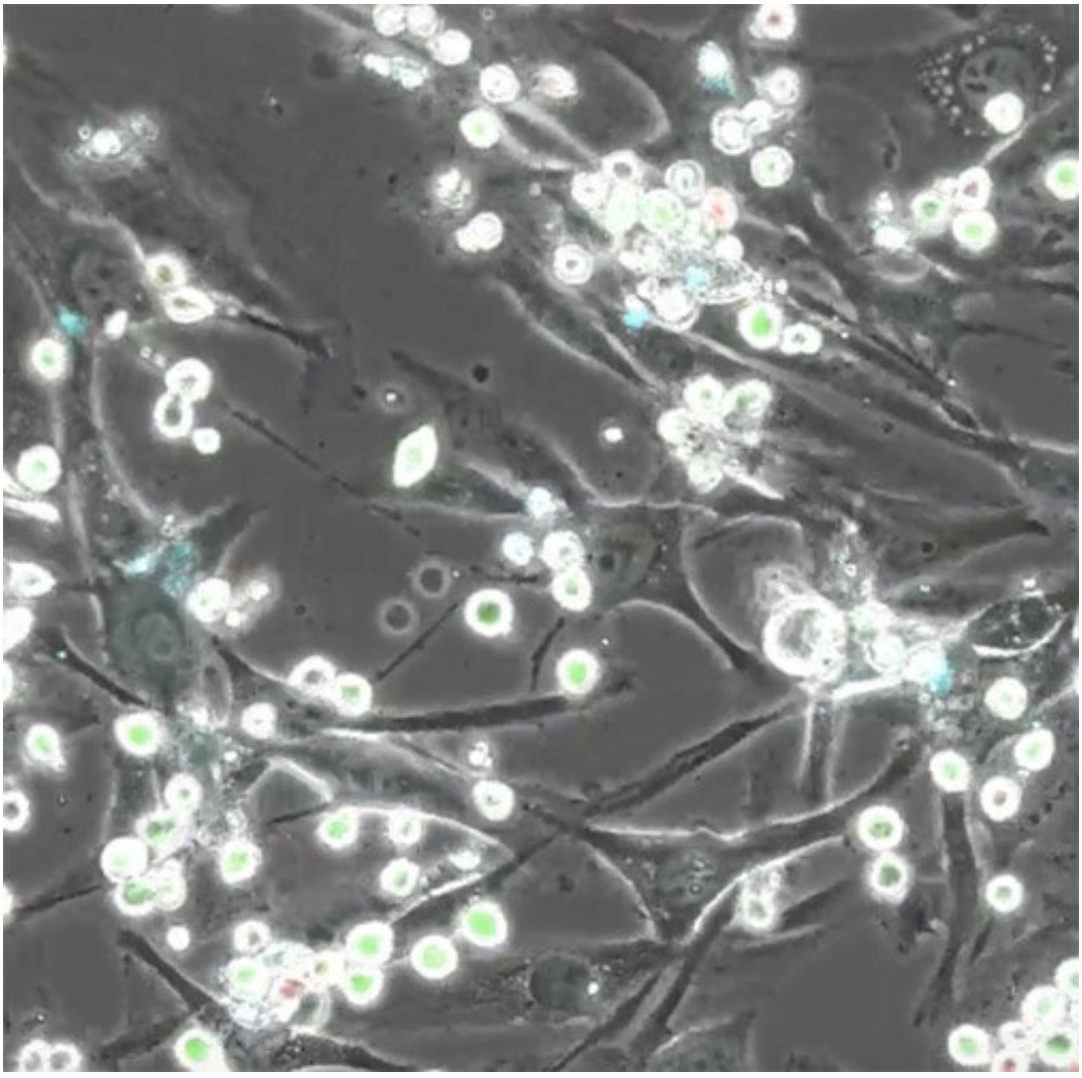

Human myeloma cells grown in a bone marrow-like microenvironment. Credit: UC San Diego Health

Multiple myeloma is the second most common blood cancer in the United States. Thirty to 50 percent of multiple myeloma patients have extra copies of the gene that encodes the enzyme ADAR1. Using a database of multiple myeloma patient samples and information, researchers at University of California San Diego School of Medicine found that high ADAR1 levels correlate with reduced survival rates. They also determined that blocking the enzyme reduces multiple myeloma regeneration in experimental models derived from patient cancer cells.

The study, published December 4 in *Nature Communications*, also suggests that a class of commercially available drugs could be used to dampen ADAR1 activity, and ultimately prevent progression or relapse in multiple myeloma.

"Despite new therapies, it's virtually inevitable that a patient with multiple myeloma will experience relapse of the disease at some point," said senior author Catriona Jamieson, MD, PhD, professor of medicine, Koman Family Presidential Endowed Chair in Cancer Research and chief of the Division of Regenerative Medicine at UC San Diego School of Medicine. "That's why it's exciting that this discovery may allow us to detect the disease earlier, and address the root cause."

The enzyme at the center of this study, ADAR1, is normally expressed during fetal development to help blood cells form. ADAR1 edits the sequence of RNA, a type of genetic material related to DNA. By swapping out just one RNA building block for another, ADAR1 alters the carefully orchestrated system cells use to control which genes are turned on or off at which times.

ADAR1 is known to promote cancer progression and resistance to therapy. In previous studies, Jamieson's team described ADAR1's contributions to leukemia. The enzyme's RNA-editing activity boosts

cancer stem cells—a special population of cells that can self-renew, giving rise to cancer, increasing recurrence and allowing some cancers to resist treatment.

In their current study, the team investigated ADAR1's role in multiple myeloma. Analyzing a database of nearly 800 multiple myeloma patient samples, they discovered that 162 patients with low ADAR1 levels in their tumor cells survived significantly longer over a three-year period compared to 159 patients with high ADAR1 levels. While more than 90 percent of patients with low ADAR1 levels survived longer than two years after their initial diagnosis, fewer than 70 percent of patients with high ADAR1 levels were alive after the same period of time.

To unravel exactly how ADAR1 is connected to disease severity at a molecular level, the researchers transferred multiple myeloma patient tissue to mice, creating what's known as a xenograft or "humanized" model.

"This is a difficult disease to model in animals—there isn't a single gene we can manipulate to mimic multiple myeloma," said co-senior author Leslie A. Crews, PhD, assistant professor at UC San Diego School of Medicine. "This study is important, in part because we now have a new xenograft model that will for the first time allow us to apply new biomarkers to better predict disease progression and test new therapeutics."

Using their new model, Jamieson, Crews and team found that two events converge to activate ADAR1 in multiple myeloma—a genetic abnormality and inflammatory cues from the surrounding bone marrow tissue. Together, these signals activate ADAR1, which edits specific RNA in a way that stabilizes a gene that can make cancer stem cells more aggressive.

They also found that silencing the ADAR1 gene in the xenograft model reduced multiple myeloma regeneration. Five to 10-fold fewer tumor cells were able to self-renew in mice lacking ADAR1, suggesting a new therapeutic target.

Clinical trials that specifically test ADAR1-targeted therapeutics for their safety and efficacy against multiple myeloma are still necessary before this approach could become available to patients. To advance their initial findings, Jamieson and Crews are exploring ways to leverage ADAR1 to detect multiple myeloma progression as early as possible. They are also testing inhibitors of JAK2, a molecule that influences ADAR1 activity, for their ability to eliminate cancer stem cells in multiple myeloma models. Several JAK2 inhibitors have already been approved by the FDA or are currently in clinical trials for the treatment of other cancers.

"Several major advances in recent years have been good news for multiple myeloma patients, but those new drugs only target terminally differentiated cancer cells and thus can only reduce the bulk of the tumor," said Jamieson, who is also deputy director of the Sanford Stem Cell Clinical Center, director of the CIRM Alpha Stem Cell Clinic at UC San Diego and director of stem cell research at Moores Cancer Center at UC San Diego Health. "They don't get to the root cause of disease development, progression and relapse—cancer stem cells—the way inhibiting ADAR1 does. I like to call our approach 'precision regenerative medicine.'"

More information: Elisa Lazzari et al. Alu-dependent RNA editing of GLI1 promotes malignant regeneration in multiple myeloma, *Nature Communications* (2017). DOI: 10.1038/s41467-017-01890-w