Senescence in liver cells can provoke a beneficial immune reaction

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Although post-reproductive life in humans is often associated with decline and a loss of powers, an analogous state in certain cells -- called senescence -- is proving to be one of ironic potency. Scientists at Cold Spring Harbor Laboratory (CSHL) today reported that a particular class of senescent liver cells orchestrates a sequence of events in living mice that can limit fibrosis, a natural response of the liver to acute damage.

The surprising finding follows on the heels of experiments conducted by the same CSHL team last year linking senescence in liver cells with the organ's ability to fight off liver cancer, also called hepatocellular carcinoma, or HCC.

The new findings are the first to establish a specific role for cellular senescence in a non-cancer pathology, and, the CSHL team notes, suggests a new therapeutic approach that could help human patients with precursors of serious liver diseases such as cirrhosis, which is the 12th most common cause of death in the United States.

Anti-cancer role of senescence provides an example

In technical terms, cellular senescence is described by team leader Scott W. Lowe, Ph.D. as "a stable form of cell-cycle arrest." By this he means senescent cells are typically ones that no longer actively divide. Senescence is therefore a highly stable state, as exemplified by benign moles in which senescent cells can persist without dividing over the

course of an entire human lifetime.

Dr. Lowe, a CSHL Professor and Howard Hughes Medical Institute Investigator, was drawn almost inexorably to this curiously quiet cellular state for its potential implications in cancer research, the prime focus of his work. Lowe's team last year demonstrated that activity of p53, a potent gene that suppresses tumor formation, also promotes senescence.

While it seemed to make sense that a very stable state in which cells don't divide could work against processes that cause cells to divide uncontrollably -- the hallmark of cancer -- it was the mechanics of the linkage that surprised Lowe's team. When they activated p53 in mice with HCC, tumors receded -- and this regression was associated directly with activation of the immune system, whose killer cells were drawn to tumors to "clear" the senescent cells.

Lowe's new work, to be reported August 22 in the journal *Cell,* reveals something analogous that is no less surprising: senescent cells located in areas of damaged liver tissue called fibroses similarly provoke a beneficial immune reaction. This reaction, involving NK, or natural killer cells, and other components of the innate immune system, serve to limit fibrotic lesions and curtail episodes of induced acute liver damage in mice.

The role of senescence in liver fibrosis

Lowe's team studied the relation of senescence to liver disease in two very different contexts: one in which damage to liver tissue was acute and another in which the damage was chronic. These contrasting experiments served to define how senescence could help limit damage, and how, when the senescence process was overwhelmed by chronic damage to the liver, tissue damage could accelerate out of control.

In experiments designed to mimic damage caused by acute insults, the CSHL scientists administered a toxin to the murine liver and observed a consistent pattern: the death of liver cells, or hepatocytes, followed by the rise of fibrotic lesions -- part of the body's natural reaction, in mice as in humans, to tissue damage. These fibroses were specifically generated by activated stellate cells, or HSCs, that proliferated in direct response to liver cell death.

Subsequent steps were of greatest interest: "After we observed the HSC cells to proliferate intensely," Dr. Lowe said, "we found that eventually they senesced and were cleared from the liver, to protect it from an excessive fibrogenic response to acute injury."

Several therapeutic mechanisms simultaneously engaged

Just as in liver cancer, the role of senescence in limiting fibrosis was two-pronged. "Cell-cycle arrest in the cells that generate the fibrosis places a kind of brake on the process, limiting how far it can go," Lowe explained. "We hypothesize that HSCs, when they senesce, secret less fibrogenic protein and also stimulate a process that tends to degrade proteins that are still present in a lesion." Lowe's team proposes that senescent cells accomplish this in part by increasing the activity of genes that stimulate the immune system.

Thus, just as senescent liver cells can play a role in tumor regression by stimulating an immune reaction, so can senescent HSCs in damaged liver tissue help clear the fibrosis by calling immune system killer cells to the scene of the damage. In such a scenario, "senescence is a kind of homeostatic mechanism that enables the tissue to return to its pre-damaged state," Lowe noted. "This may prove to be broadly relevant to other wound-healing processes."

Senescence overwhelmed: the lesson of chronic tissue damage

In marked contrast, separate experiments in mice that modeled chronic liver damage, such as that caused by alcoholism, chronic hepatitis, or fatty liver disease, showed that the mice produced senescent cells more rapidly than they could be "cleared." According to Lowe, this resulted in "persistent inflammation and advancing fibrosis" -- a state that can lead to cancer in some instances.

Considered together, the results of the experiments in chronic vs. acute fibrosis suggest, in the chronic instance, how fibrosis can lead to cirrhosis, a predisposing condition for the genetic mutations and other cellular transformations that cause liver cancer. But in the acute instance, the experiments suggest that future therapy designed to stimulate the immune cells that target senescent cells in fibrotic lesions may provide effective treatment for patients with acute liver damage, particularly in its early stages following short-term exposure to toxic agents.

Source: Cold Spring Harbor Laboratory