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An anti-aging protein could be targeted to rejuvenate immune cells

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Anti-aging proteins have long been shown to protect against age-related diseases, such as cancer, neurodegeneration, and cardiovascular disease. A study by researchers at the Gladstone Institutes now reveals that one such protein could also be targeted to rejuvenate cells in the immune system.

The protein in question is called SIRT1, more commonly known for being activated by red wine. In the new study, published in the *Journal of Experimental Medicine*, the scientists found that it is also involved in how cells in the immune system develop with age.

They wanted to find out how this anti-aging protein affects a specific category of immune cells known as cytotoxic T cells. These cells are highly specialized guardians of the immune system and their role is to kill cells infected by a virus, damaged cells, or cancer cells.

"Over the course of a person's life, with repeated exposure to bacteria and viruses, these T cells mature and eventually lose a protein called CD28," said Gladstone Senior Investigator Melanie Ott, senior author of the new study. "And as these cells get older, they become more toxic to their environment."

This aging process is accelerated by persistent viral infections, such as HIV and CMV (human cytomegalovirus). In fact, HIV-infected patients accumulate mature cytotoxic T cells at a much younger age than an uninfected person.

"A higher number of mature cytotoxic T cells in the body has been associated with age-related, autoimmune, and inflammatory diseases," added Ott, who is also a professor in the Department of Medicine at the UC San Francisco. "We wanted to come up with a way to counteract this phenomenon."

What Happens in Aging Cells

When a young (or naive) T cell is in a resting state, it uses oxygen to "breathe". Once it is activated to defend the body against a bacteria or virus, it shifts into enhanced glycolysis and uses sugar to get an immediate boost in energy. This is useful to jump into action, but it isn't sustainable for long-term performance.

"You can think of it like a 60-meter sprint runner who needs a quick boost of energy to finish the race, in comparison to a marathon runner who needs different energy sources to keep going for a long period of time," said Ott.

As the cells age and lose CD28, they can shift into glycolysis much more quickly if breathing is inhibited. They also lose the anti-aging protein SIRT1. This becomes a problem, as it makes them more toxic to the cells around them.

In the new study, Ott and her team finally explain how this all happens.

"We studied human T cells, isolated from blood donors of all ages, to compare mature cytotoxic T cells with naive ones," said Philip Ansumana Hull, graduate student in Ott's lab and one of the first authors of the study.

They found that naive T cells have a high concentration of SIRT1. This stabilizes an entire mechanism that prevents the cells from entering

glycolysis to use sugar as an energy source, and limits their toxic effects.

As the cells age, they lose SIRT1, which changes their basic metabolism. They can then rapidly shift into glycolysis and start producing more toxic proteins called cytokines, which could lead to inflammatory diseases.

One Mechanism to Fight Both Aging and Aggressive Tumors

Based on a better understanding of the crucial role played by SIRT1 in the aging of T cells, the researchers identified two potential new drug targets.

First, new drugs could be developed to strengthen SIRT1 to rejuvenate mature cytotoxic T cells or keep them from progressing too quickly into a highly toxic state.

"This could postpone the development of age-related diseases," said Mark Y. Jeng, the study's other first author and former graduate student in Ott's lab. "It could also help people with a weaker immune system fight infections or better respond to immune vaccination, such as seniors or chronically-infected patients."

Alternatively, drugs could be used to obtain the opposite effect and encourage the T cells to be more toxic. By temporarily making young T cells more aggressive and behave like mature cells, they could, for example, support an aggressive anti-tumor response or other immune therapeutic approaches.

More information: Mark Y. Jeng et al. Metabolic reprogramming of human CD8+memory T cells through loss of SIRT1, *The Journal of Experimental Medicine* (2017). DOI: 10.1084/jem.20161066

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