A Mechanism that Eliminates Senescent Cells

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We are learning how immune cells naturally clear the body of senescent cells that contribute to aging and many chronic diseases. Understanding this process may open new ways of treating age-related chronic diseases with immunotherapy.

In a healthy state, these immune cells (known as invariant Natural Killer T (iNKT) cells) function as a surveillance system, eliminating cells the body senses as foreign, including senescent cells, which have irreparable DNA damage. But the iNKT cells become less active with age and other factors like obesity that contribute to chronic disease.

Finding ways to stimulate this natural surveillance system offers an alternative to senolytic therapies, which to date have been the primary approach to removing senescent cells. It could be a boon to a field that has struggled with how to systemically administer these senolytics without serious side effects.

The iNKT cells have two attributes that make them an especially appealing drug target. First, they all have the same receptor, which does not appear on any other cell in the body, so they can be primed without also activating other types of immune cells. Second, they operate within a natural negative feedback loop that returns them to a dormant state after a period of activity.

"Using iNKT-targeted therapy can piggyback on their exquisite, built-in specificity," said Anil Bhushan, PhD, a professor at Diabetes Center and senior author of the paper from *Med* a new journal from Cell Press which publishes clinical and translational research articles firmly rooted in therapeutic impact.

The scientific team found they could remove senescent cells by using lipid antigens to activate iNKT cells. When they treated mice with diet-induced obesity, their blood glucose levels improved, while mice with lung fibrosis had fewer damaged cells, and they also lived longer.

Mallar Bhattacharya, MD, associate professor of medicine at UCSF who treats patients with lung disease and is an author of the paper, said the results presented for iNKT cells in a mouse model of lung fibrosis offer hope for a potentially fatal disease that often leads to lung transplants.

"I think this is a potential immune therapy for senescence and fibrosis," Bhattacharya said. "It's a fairly well tolerated therapy, and we just have to get around dosing and trials."

A diabetes researcher, Bhushan first started paying attention to iNKT cells when a previous study identified a link between iNKT cells and senescent pancreatic beta cells. Because senescent cells tend to accumulate in many tissues and correlate with disease, he surmised that activating iNKT cells could be used to treat a wide variety of diseases.

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A biotech company that Bushan helped found, Deciduous Therapeutics, Inc., is planning to translate this early discovery to the clinic in the next few years.

Additional co-authors include Peter Thompson, Shivani Arora, Yao Wang, Aritra Bhattacharyya, Hara Apostolopoulou, Ram Naikawadi, Paul Wolters and Suneil Koliwad, all of UCSF; and Rachel Hatano and Ajit Shah of Deciduous.

The research was supported by the Larry L. Hillblom Foundation, the Diabetes Research Connection, the UCSF Sandler Asthma Basic Research Center, the UCSF Diabetes Center and NIH R01DK121794 and R01DK118099.

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