

“Black Hole” Formed by Aging Cells Hobbles Key Immune Organ’s Function and Regeneration

Non-functional cells accumulate in the aging thymus; this may impair cancer treatment, vaccine efficacy, immune function and more.

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Scientists hoping to discover better ways to boost immune function — which could lengthen our healthspan and protect immunocompromised patients — may have a new target, according to findings published August 7 in *Nature Immunology*. Investigators at Fred Hutch Cancer Center, Memorial Sloan Kettering Cancer Center (now based at City of Hope), and WEHI (based in Melbourne, Australia), described a [novel cell type that only emerges with age](#) and appears to contribute to age-related waning of immunity.

Located in a critical immune organ called the thymus, the new cells appear superficially like supportive cells that are essential to our immunity. But instead, the aging, ineffectual cells crowd out normal cells and soak up regenerative factors. As they increase in numbers, they sabotage the thymus’ ability to produce new immune cells and regenerate after damage.

“Thymic function is important throughout our life, but its declining function contributes to poor immunity,” said Fred Hutch thymus and regenerative medicine expert [Jarrod Dudakov, PhD](#). “Our findings highlight a novel biological feature of aging, but they also offer an innovative target to therapeutically boost thymic function.”

Dudakov is a co-senior author with WEHI immunologist [Daniel Gray, PhD](#), and bone marrow transplant expert [Marcel van den Brink, MD, PhD](#) (formerly at MSK, now president of City of Hope Los Angeles and its National Medical Center).

Strategies that counteract thymic aging and its decline in function could have big implications for human health, Dudakov said. Such therapies could improve immune recovery (and infection protection) after bone marrow transplant (in which a patient’s immune system is nearly obliterated). They could also help maintain vaccine responses throughout our lifespans.

Thymus-targeting therapies may also improve efficacy for various cancer immunotherapies, such as [checkpoint inhibitors](#) that can release the brakes on anti-cancer immune responses, Dudakov

said.

The thymus: critical immune incubator

The thymus (not to be confused with the thyroid) nestles just above and in front of the heart, right between the lungs' lobes. Despite its small size, it's critical to our health: The thymus is where a specialized type of infection- and cancer-fighting cell, called the T cell, develops.

"The thymus has two main roles," Dudakov said.

Its first role is to ensure that a person has a broad range of T cells able to counter the incredibly diverse (and unknown) set of pathogens or tumor mutations that the person could potentially encounter. The thymus' second role is to keep us safe from ourselves, by preventing autoimmunity.

Both roles relate to the T-cell receptor, or TCR, which T cells use to recognize their targets. Each new T cell's TCR is unique, stitched together from a selection of genetic elements. In theory, a single person's T cells could create quintillions of TCRs. This is great news in the battle we wage against infections.

"But most of what [new TCRs] will recognize are our own proteins," Dudakov said. Allowed to roam free, these T cells would attack our own tissues and cause autoimmunity.

"So you've got to 'educate' those T cells to say, 'You want to recognize these targets, but not those targets.' That requires a really specialized organ," he said.

Age comes for the thymus

But despite its central importance to our health, the thymus is one of the first organs to show its age. Nimble and quick in childhood, it's tripped up by the onrush of sex hormones at puberty. Post-pubertal thymuses never churn out T cells at the same rate as before.

As the years pass, the thymus slowly shrinks and gets, well, a little flabby. Eventually — no matter how fit the person — much of its T-cell nurturing tissue will be replaced by fat. The thymus educates fewer T cells, and fewer T cells means there are more and more "holes" that pathogens or cancer cells can slip through. This age-related decline contributes to less robust vaccine responses and protection against infection in older adults.

The thymus also loses a step in the face of common triggers like stress or infection. It balances this sensitivity with a surprising ability to regenerate: It can bounce back (eventually) even after damage from chemotherapy or radiation treatment. But this elasticity also wanes with age.

Therapies that help maintain thymic function and regenerative capacity could do a lot to keep us

healthy over our lifetimes and in times of need, such as cancer treatment. They could improve vaccine efficacy or help vulnerable bone marrow transplant patients (whose immune systems are cleaned out to make room for healthy donor bone marrow) regain immune protection more quickly.

Aging thymic cells retire early

The cells that “mentor” developing T cells are called thymic epithelial cells, or TECs. We know that TECs get replaced by adipose cells as we age, but there’s a lot left to learn about other age-related changes in the thymus.

The work builds on a foundational history in immunology and bone marrow transplantation: BMT, a Nobel Prize-winning approach to treating blood cancers, was [developed at Fred Hutch](#), while WEHI investigators [demonstrated the thymus’ central role in immunity](#).

The current project grew out of a long-standing collaboration with van den Brink’s team, Dudakov and Fred Hutch/City of Hope computational biologist Anastasia Kousa, PhD. Formerly at Fred Hutch and MSK, Kousa is co-first author with City of Hope immunologist Lorenz Jahn, PhD (formerly at MSK), and WEHI immunologist Kelin Zhao, PhD.

As part of the collaboration, Dudakov and Kousa examined individual thymic cells from mice aged one month to 18 months. Single-cell sequencing technologies open a window into the genes that individual cells have turned on and off. This can reveal a cell’s role and what it’s doing (or failing to do). Kousa and Dudakov used computational analyses to describe cell populations in mouse thymuses of different ages.

“We found that with age there seems to be kind of this alternate-lineage differentiation of thymic epithelial cells,” Dudakov said. “They kind of look like TECs, but they’re not TECs.”

He and Kousa dubbed these cells age-associated TECs, or aaTECs. Not yet replaced by fat, aaTECs have apparently decided to “retire” early. No longer do they help educate T cells or help repair damage. They appear to be undergoing an identity crisis, showing lower expression of certain genes that are TEC hallmarks.

Zhao, on Gray’s team, used innovative thick-slice microscopy on mouse thymus tissue to enable the collaborators to see non-functional regions that appear to correspond to the aaTECs Kousa and Dudakov had described. Though still rich in epithelial cells, these areas lack T cells.

Age-associated TECS “exist in very tight clusters — so tight that they barely allow any other cells to enter that space,” Kousa said. “This prompted us to characterize these areas as thymocyte [developing T-cell] ‘deserts.’ In order for the thymus to function properly, it heavily relies on different cell types (the majority of which are thymocytes) interacting with and contacting each other.”

The tight clusters of aaTECs “creates these nonproductive niches within the thymus — we call them scars, essentially — that are not supportive of T cell development,” Dudakov said.

With time, the islands where T cells can find the guidance they need grow smaller and smaller.

With Duke University collaborator [Laura Hale, MD, PhD](#), the team showed that similar regions of lackluster TECs appear to sprout and grow in human thymuses as well.

“We can’t say with 100% conclusiveness that they are the same thing, but the same features that exist in an aging human thymus seem to exist in these mice,” Dudakov said.

Not content to shirk T-cell education, aaTECs also appear to drain thymic resources. This, in turn, stymies the thymus’ ability to regenerate. The investigators tracked restoration of thymic function after treating mice with whole-body irradiation (which mimics the preconditioning regimen that bone marrow transplant patients undergo).

It took about 28 days for thymic function to recover in one- to two-month-old mice, but 42 days for thymuses of 18-month-old mice to recover. When the scientists looked closely at cells from aged thymuses, they found that aaTECs had gained ground, and made up a larger proportion of cells than before the radiation treatment. They saw similar results — and more aaTECs — in mice from University of Georgia co-author [Nancy Manley, PhD](#), which have been genetically manipulated so their thymuses age at a faster-than-average rate.

“The aaTECs are a bit like a black hole,” Dudakov said.

The aaTECs are the second jab in a “one-two punch” for aging thymuses, he said. Aging thymuses produce lower amounts of regenerative factors to begin with, and then the aaTECs “steal whatever [regenerative] signals are left, so you’re left with even less to support the normal TECs,” Dudakov said.

Next: untangling how aaTECs arise, how to target them

There remains much to be discovered about aaTECs and their role in the decline of immunity with age, Dudakov said.

“We’ve still got to figure out when does it start and how does it start,” he said.

The scientists are also working to validate their findings — both the presence of aaTECs and their influence on thymic function — with human data, Kousa said. This will create new avenues to pursue to improve immune function, particularly in older people, she said.

“Having identified this age-related cell population, we are now better equipped to design experiments to directly target this population in an effort to restore this part of the organ to a functional state,” Kousa said.

The team is working to uncover the molecular mechanisms underlying the rise of aaTECs, and whether these biological underpinnings present potential therapeutic targets.

“The molecular mechanism and therapeutic targeting are really two sides to the same coin,” Dudakov said. “By understanding one, we hope it will lead us to developing therapies for the other.”

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