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# Key differences in young, older people's immune cells attributed to environment

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Discoveries by Stanford University School of Medicine investigators may help explain why older people's immune systems often don't work so well, why different people's immune systems age at different rates,

and why the environment matters more than heredity in generating these age-related differences.

The findings, which could lead to new ways of putting the brakes on aging and disease, were enabled by a technological innovation: a fast, accurate way to tell what proteins single cells are being instructed to produce, and the degree to which separate cells of the same type have received differing versions of those instructions. Using this new method to analyze hundreds of millions of immune cells one by one, the researchers found that older people's immune cells get a fuzzier set of marching orders than do those of younger people.

In a study to be published April 26 in *Cell*, the scientists focused on chemical marks affixed to proteins called histones, which closely associate with DNA in the cell nuclei of all living creatures that aren't bacteria or closely related one-celled organisms.

It's known that these so-called epigenetic marks are more than mere graffiti. "They're instructions rendering stretches of DNA—and the genes residing in those stretches—alternatively accessible or off-limits to the massive mobile molecular machines that read our genes. Ultimately, they orchestrate the production of the proteins our genes encode," said PJ Utz, MD, professor of immunology and rheumatology. Utz shares senior authorship of the study with Purvesh Khatri, Ph.D., assistant professor of biomedical informatics and of biomedical data science, and with basic life science research associate Alex Kuo, Ph.D. Lead authorship is shared by basic life science research associate Peggie Cheung, Ph.D., and postdoctoral scholar Francesco Vallania, Ph.D.

## Epigenetic influence

Proteins are the workhorses that carry out the bulk of a cell's activities, so a cell's identity and agenda are intimately tied to the types and

amounts of proteins that are active inside it. While virtually every cell in your body contains the same DNA, your skin cells, fat cells and nerve cells differ vastly from one another in their protein content and, therefore, in their function. By specifying which genes are to be active or quiescent, the constellation of epigenetic marks along a cell's DNA largely directs and defines the cell's overall behavior.

These marks, moreover, are in flux; unlike our more-or-less unchanging genes, they can be rapidly affixed to or expunged from histones upon a cell's exposure to pathogens, nutrients, growth factors or hormones, or upon changes in the cell's internal state—for example, when it's time for the cell to undergo division, or as the cell ages. The cell's protein output, and its work agenda, change in response.

"Barring the odd mutation or some fraying of the tips of your chromosomes, your DNA stays essentially the same as you get older," said Khatri. "But while for the most part our genes don't change much as we age, how active each of them is can change quite considerably in either direction over time."

In particular, the numerous types of white blood cells in our immune systems show marked changes in gene-activation levels as we age. We also know that as we age, our immune system usually doesn't work so well, Khatri noted.

"The immune system plays a prominent role in all kinds of diseases," he said. "By focusing too heavily on genetics, we're ignoring the implications of human immunology and environmental influences that act on it."

The Stanford team hypothesized that aging-related changes in immune cells' genes might arise from flux in the pattern of epigenetic marks on the cells' histones. They set out to determine whether and how much, for

any given immune cell type, these patterns diverged between different people or between different individual cells of the same type in any single person's blood.

## Analyzing single cells

To make these determinations, the scientists modified a technique called mass cytometry. This method allows multiple features of a single cell to be characterized simultaneously as specialized molecular barcodes that have been attached to it strike a detector, revealing not only the cell's identity but also its state—for example, immature versus mature, or activated versus quiescent. The cells are incinerated and their remains flung at a detector in rapid-fire sequence. Although the cells themselves have gone up in smoke, their incombustible barcodes hit the detector and are identified and catalogued. In this way, the individual identities and states of huge numbers of cells can be quickly ascertained.

For the study, Kuo and Cheung spent more than a year designing molecular barcodes that would permit mass cytometry to specify the amounts of each of 40 different types of epigenetic marks and 30 additional identifying features in 22 different immune cell types, and more than another year conducting experiments with them. In all, the ensuing experiments generated some 21.7 billion data points. Vallania devised specialized techniques for analyzing this huge bolus of information.

The researchers found that for many of the immune-cell types, older people's cells bore, on average, substantially more histone marks than those of younger ones. In addition, older people showed more cell-to-cell variation in how much their histones were marked up than did younger people.

Then, to assess environmental versus genetic influences on histone

marking patterns, the researchers obtained blood samples from identical and fraternal twin pairs. Identical twins share the same DNA sequences. They also share a common intrauterine environment, and, if raised together, reasonably similar childhood environments; fraternal twins, although their DNA is no more similar than that of typical siblings, share their intrauterine and, if raised together, childhood environments.

Histone-marking patterns between older identical twins diverged substantially more from one another than those in younger twin pairs. The differences between older identical twins were effectively equal to the differences between genetically unrelated people. Data analysis indicated that the observed histone-mark divergence among older people comes from nonheritable factors: food, sleep, exercise, infections, our jobs, what city we live in, and other sources of physical or psychological stress and relief that act on us throughout our lives.

Medications targeting the enzymes that affix some histone marks are approved for some cancer indications. Utz and Khatri are now examining histone-marking patterns of other diseases to see if any are characterized by elevated or diminished levels of specific types of marks. They speculate that histone-mark analysis may lead to drugs that, by reversing histone-mark deviations from the healthy state, could treat diseases characterized by those deviations.

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