Researchers use single-cell sequencing to understand how cells age

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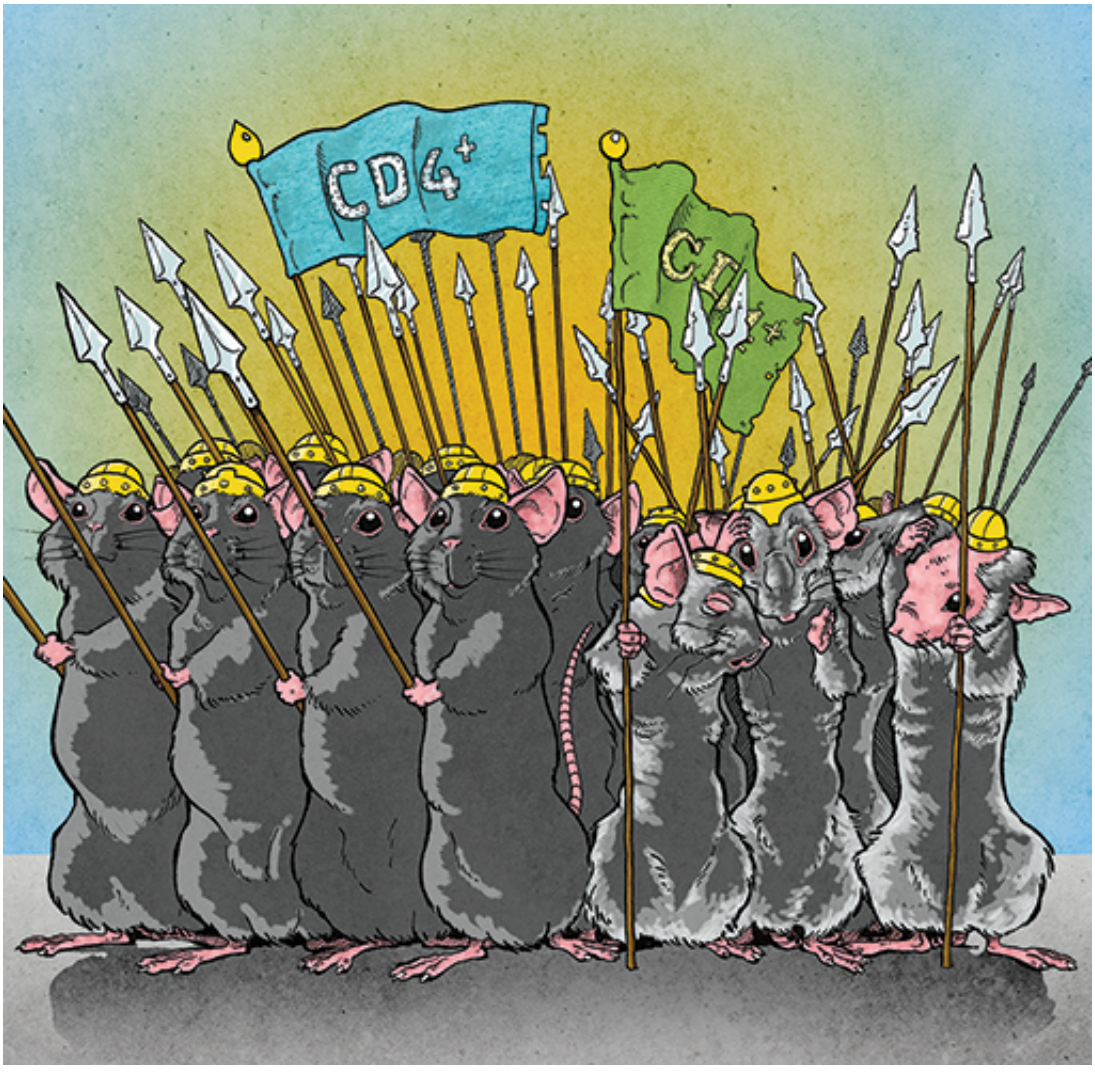

A new EMBL-EBI study reveals that aging causes cell coordination breakdown. Credit: Spencer Phillips, The European Bioinformatics Institute

Researchers from the European Bioinformatics Institute (EMBL-EBI), University of Cambridge, the Wellcome Trust Sanger Institute and the Cancer Research UK-Cambridge Institute (CRUK-CI) have shed light on a long-standing debate about why the immune system weakens with age. Their findings, published in *Science*, show that immune cells in older tissues lack coordination and exhibit much more variability in gene expression compared with their younger counterparts.

Settling the debate

We've all witnessed the progressive decline of function that comes with ageing, but what exactly causes this decline - and why does it happen at different rates for different parts of the body? To find answers, scientists need to unpick all of the mechanisms of ageing at the molecular level, for every tissue. Today's study focused on immune tissue: specifically, CD4+ T cells.

The immune system is like a symphony orchestra, with many different types and subtypes of cells working together to fight infections. But as the immune system ages, its response to infection weakens for reasons that are not yet clear. One long-standing debate amongst scientists concerns two central hypotheses: either the functional degradation is caused by a loss of cellular performance, or it is down to a loss of coordination among cells.

To resolve the debate, scientists have studied many different cell types, analysing 'average' gene expression profiles. Today's study employed high-resolution single-cell sequencing technology to create new insights into how cell-to-cell variability is linked with ageing. The researchers sequenced the RNA of naïve and memory CD4+ T cells in young and old mice, in both stimulated and unstimulated states.

Their findings clearly showed that loss of coordination is a key

component of the impaired immune performance caused by T cell ageing.

The DNA smoothie

"You could think of DNA sequencing as a fruit smoothie," explains John Marioni, Group Leader at EMBL-EBI and at CRUK-CI. "Traditional sequencing technology is a bit like taking a sip of the smoothie, then trying to guess what the ingredients are. Single-cell genomics now lets us study the ingredients individually, so we get direct insight into the constituent parts. Extrapolating, this means that single-cell sequencing allows researchers to individually look at thousands of genes at any given time."

A phalanx of immune cells

Duncan Odom, Group Leader at the University of Cambridge's Cancer Research UK Cambridge Institute and associate faculty at the Wellcome Trust Sanger Institute, shares a further analogy to explain how immune cells fight infection.

"Imagine the immune system as a 'cell army', ready to protect the body from infection," says Odom. "Our research revealed that this army is well coordinated in young animals, with all the cells working together and operating like a Greek phalanx to block the infection."

Odom goes on to explain that this tight coordination makes the immune system stronger, and allows it to fight infection more effectively. The team's study shows that as the animal gets older, cell coordination breaks down.

"Although individual cells might still be strong, the lack of coordination

between them makes their collective effectiveness lower," Odom concludes.

Older and more variable

Previous studies have shown that in young animals, immunological activation results in tightly regulated gene expression (see Box). This study further reveals that activation results in a decrease in cell-to-cell variability. Ageing increased the heterogeneity of gene expression in populations of two mice species, as well as in different types of immune cells. This suggests that increased cell-to-cell transcriptional variability may be a hallmark of ageing across most mammalian tissues.

"There is a great deal of interest in how biological ageing happens, but not much is known about molecular ageing," says Celia Pilar Martinez-Jimenez, experimental lead and Postdoctoral Fellow at the Sanger Institute and CRUK-CI. "This research initiative explored a new facet of cell response to disease, while also tackling questions related to ageing."

Nils Eling, computational lead of the project and PhD student at EMBL-EBI and CRUK-CI highlights that "the advantage of analysing gene expression from single cells is to detect how cell populations synchronise their response. It is interesting to see that ageing strongly distorts this response - a phenomenon which could not be observed before."

The interdisciplinary study paves the way for a more in-depth exploration of the mechanisms by which different types of cells age. It also illustrates the potential of single-cell sequencing to enable a richer understanding of cell development and activity.

More information: Martinez-Jimenez, C.P., Eling, N.et al (2017) Aging increases cell-to-cell transcriptional variability upon immune stimulation. *Science*. Published in print. science.sciencemag.org/cgi/doi

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