Team identifies IL-17 protein as key factor in skin aging

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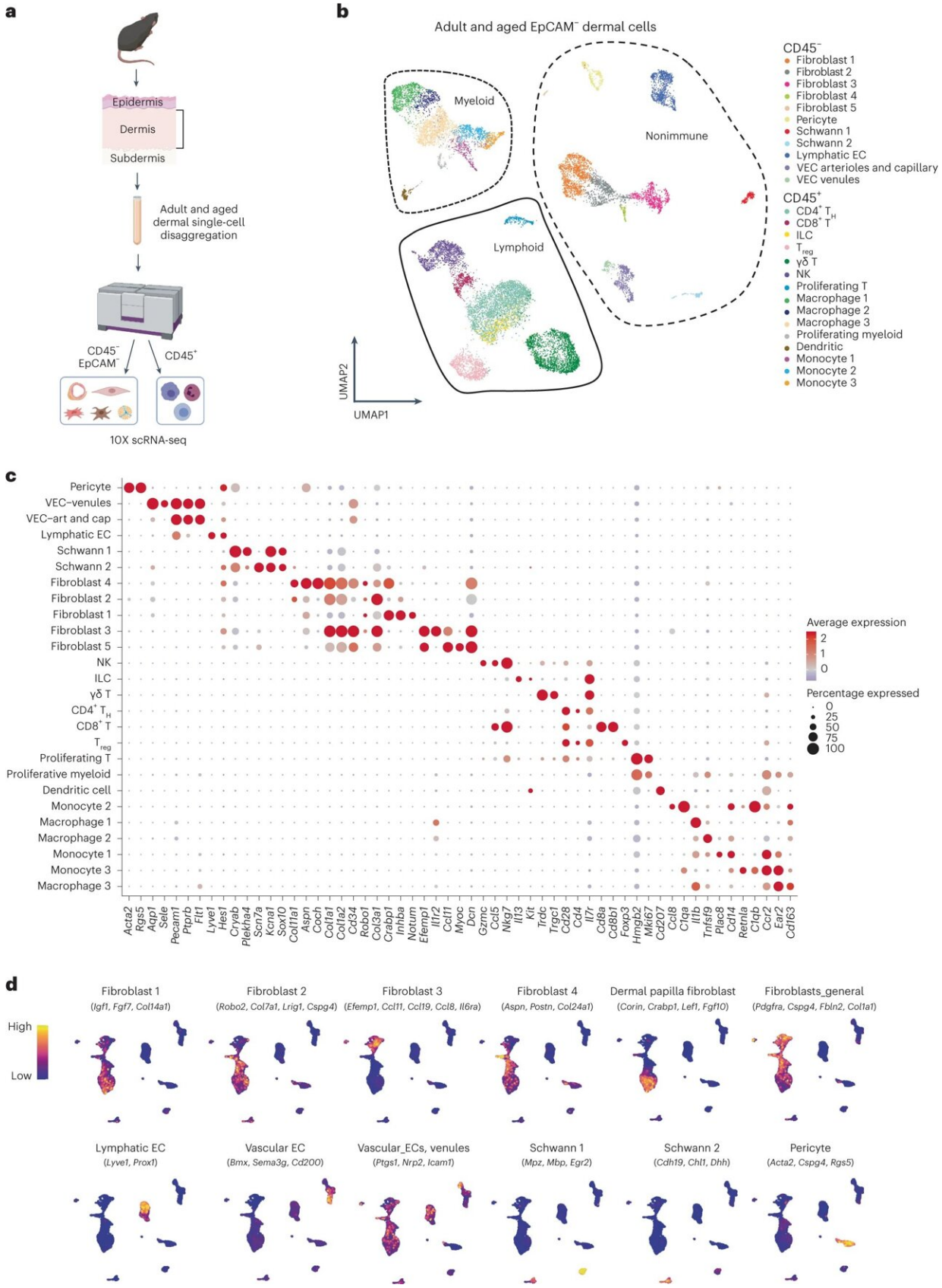
a
Epidermis
Dermis
Subdermis
Adult and aged dermal single-cell disaggregation
CD45⁻ EpCAM⁻
CD45⁺
10X scRNA-seq
b
Adult and aged EpCAM⁻ dermal cells
Myeloid
Nonimmune
Lymphoid
UMAP2
UMAP1
CD45⁻
Fibroblast 1
Fibroblast 2
Fibroblast 3
Fibroblast 4
Fibroblast 5
Pericyte
Schwann 1
Schwann 2
Lymphatic EC
VEC arterioles and capillary
VEC venules
CD45⁺
CD4⁺ T_H
CD8⁺ T
ILC
T_reg
γδ T
NK
Proliferating T
Macrophage 1
Macrophage 2
Macrophage 3
Proliferating myeloid
Dendritic
Monocyte 1
Monocyte 2
Monocyte 3
c
Pericyte
VEC–venules
VEC–art and cap
Lymphatic EC
Schwann 1
Schwann 2
Fibroblast 4
Fibroblast 2
Fibroblast 1
Fibroblast 3
Fibroblast 5
NK
ILC
γδ T
CD4⁺ T_H
CD8⁺ T
T_reg
Proliferating T
Proliferative myeloid
Dendritic cell
Monocyte 2
Macrophage 1
Macrophage 2
Monocyte 1
Monocyte 3
Macrophage 3
Acta2 Rgs5 Aqp1 Sele Pecam1 Ptprb Flt1 Lyve1 Hes1 Cryab Plekha4 Scn7a Kcna1 Sox10 Col11a1 Aspn Coch Col1a1 Col1a2 Cd34 Robo1 Col3a1 Crabp1 Inhba Notum Efemp1 Il1r2 Ccl11 Myoc Dcn Gzmc Ccl5 Nkg7 Il13 Kit Trdc Trgc1 Cd28 Cd4 Il7r Cd8a Cd8b1 Foxp3 Hmgb2 Mki67 Cd207 Ccl8 C1qa Il1b Tnfsf9 Plac8 Cd14 Retnla C1qb Ccr2 Ear2 Cd163
Average expression
2
1
0
Percentage expressed
0
25
50
75
100
d
High
Low
Fibroblast 1
(Igf1, Fgf7, Col14a1)
Fibroblast 2
(Robo2, Col7a1, Lrig1, Cspg4)
Fibroblast 3
(Efemp1, Ccl11, Ccl19, Ccl8, Il6ra)
Fibroblast 4
(Aspn, Postn, Col24a1)
Dermal papilla fibroblast
(Corin, Crabp1, Lef1, Fgf10)
Fibroblasts_general
(Pdgfra, Cspg4, Fbln2, Col1a1)
Lymphatic EC
(Lyve1, Prox1)
Vascular EC
(Bmx, Sema3g, Cd200)
Vascular_ECs, venules
(Ptgs1, Nrp2, Icam1)
Schwann 1
(Mpz, Mbp, Egr2)
Schwann 2
(Cdh19, Chl1, Dhh)
Pericyte
(Acta2, Cspg4, Rgs5)

Dermal cell characterization by 10X scRNA-seq. **a**, Workflow used to obtain dermal cells of adult and aged mouse back skin. Single-cell suspensions were enriched separately for $EpCAM^{-}CD45^{-}$ and $CD45^{+}$ cells by FACS. Transcriptomes of sorted single cells were then analyzed by 10X scRNA-seq. For $CD45^{+}$ cells, $n = 7$ mice for the adult group and $n = 4$ mice for the aged group, with three technical replicates; for $CD45^{-}EpCAM^{-}$ cells, $n = 2$ mice for the control group and $n = 2$ mice for the aged group, with two technical replicates. Created with BioRender.com. **b**, UMAP visualization of all adult and aged dermal cells analyzed by 10X scRNA-seq. **c**, Dot plot showing discriminatory markers for each cell type, subtype and state found in **b**. **d**, UMAP visualization of nonimmune cell subtype-specific signatures. EC, endothelial cells; VEC, vascular endothelial cells. Credit: *Nature Aging* (2023). DOI: 10.1038/s43587-023-00431-z

A team of scientists from the Institute for Research in Biomedicine (IRB Barcelona) in collaboration with the National Center for Genomic Analysis (CNAG) has discovered that IL-17 protein plays a central role in skin aging. The study, which was led by Dr. Guiomar Solanas, Dr. Salvador Aznar Benitah, both at IRB Barcelona, and Dr. Holger Heyn, at CNAG, highlights an IL-17-mediated aging process to an inflammatory state.

Skin aging is characterized by a series of structural and functional changes that gradually contribute to the deterioration and fragility associated with age. Aged skin has a reduced capacity to regenerate, poor healing ability, and diminished barrier function.

Published in the journal *Nature Aging*, this work describes the changes undergone by different types of cells with aging and identifies how some immune cells in the skin express high levels of IL-17.

"Our results show that IL-17 is involved in various functions related to aging. We have observed that blocking the function of this protein slows down the appearance of various deficiencies associated with aging skin. This discovery opens up new possibilities for treating some of the symptoms or facilitating skin recovery after surgery, for example," explains Dr. Aznar Benitah, ICREA researcher and head of the Stem Cells and Cancer laboratory at IRB Barcelona.

"Single cell sequencing has allowed us to dive deep into the complexity of cell types and states forming the skin and how these change during lifespan. We did not only find differences in the composition of aged skin, but also changes in cell activity states. Particularly immune cells showed specific age-related profiles, which we could pinpoint by analyzing thousands of individual cells on at a time," says Dr. Holger Heyn, head of the Single Cell Genomics laboratory at CNAG.

Immune cells, inflammation, and aging

In addition to a wide variety of epithelial cells, hair follicle cells, and other components, the skin is also home to immune cells, which play a crucial role in preventing infection and protecting against different damages.

The study describes how, during aging, the presence of some of these immune cells, namely gamma delta T cells, innate lymphoid cells, and $CD4^+$ T cells, significantly increases in the skin. These same cells also start expressing very high levels of the pro-inflammatory cytokine IL-17.

"Aging is associated with mild but persistent inflammation and, in the skin, this is characterized by a significant increase in IL-17, which causes skin deterioration," explains Dr. Paloma Solá, first author of the paper, together with Dr. Elisabetta Mereu, who is now a researcher at the Josep Carreras Leukemia Research Institute.

Reversing the symptoms of aging in skin

Previous studies had described that IL-17 is related to some autoimmune skin diseases, such as psoriasis, and there are existing treatments that block this protein. The team of researchers studied the response of various aspects to blocking IL-17 activity, including hair follicle growth, transepidermal water loss, wound healing, and genetic markers of aging. These four parameters showed an improvement after treatment, as the acquisition of these aging traits was significantly delayed.

"IL-17 protein is essential for vital body functions, such as defense against microbes and wound healing, so permanently blocking it would not be an option. What we have observed is that its temporary inhibition offers benefits that could be of interest at a therapeutic level," says Dr. Guiomar Solanas, associate researcher at IRB Barcelona.

Future work by the researchers will focus on clarifying the aging processes that are related to inflammatory states in the skin and how these are linked to IL-17. The team will also address whether IL-17 is involved in the aging and deterioration of other tissues and organs.

More information: Solá, P. et al, Targeting lymphoid-derived IL-17 signaling to delay skin aging, *Nature Aging* (2023). DOI: 10.1038/s43587-023-00431-z.
www.nature.com/articles/s43587-023-00431-z

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