This Old Neighborhood Made M1 this Way

Florian Gruber[1,2] and Mikolaj Ogrodnik[3,4,5]

Journal of Investigative Dermatology (2022) **142,** 3131–3132; doi:10.1016/j.jid.2022.07.014

When pttissues age, the composition and the properties of the residing cell populations change, resulting in low-grade inflammation, proteolysis, impaired nutrient sensing, and an increased number of senescent cells (López-Otín et al., 2013). Although the age-related alterations mentioned earlier seem to occur in most if not all tissues, there are also some age-related changes, which are tissue specific. For example, an accumulation of UV-induced DNA modifications or a decrease in hyaluronic acid synthesis seems to be specific to aging of skin cells and is especially pronounced in dermal fibroblast (Tigges et al., 2014). Often neglected in their importance for the aging process are changes to the extracellular matrix (ECM). Skin, among other organs, is composed first and foremost of ECM, with cells embedded between the long and elastic fibers of the matrix. Specifically, 70% of skin dry mass can be attributed to the ECM (Zhao et al., 2019), including fibers made of collagen, elastin, fibronectin, and proteoglycans, among others, with the cellular fraction providing a much smaller contribution. Despite this disproportion, majority of research omits the aspect of the cell–ECM interactions and their implications for mammalian physiology and pathology. Although the progressive aging of the environment and ECM of several tissues has been shown to impact the viability and function of cells, the description of aging-related interactions between ECM and skin cells is incomplete. The advent of single-cell and spatial sequencing technologies promotes the detailed tracking of cellular composition and has already brought groundbreaking insights, allowing to determine the dynamics of cellular phenotypes within the skin (Reynolds et al., 2021). In their new article, Gather et al. (2022) analyzed published single-cell sequencing data from the skin of young and old donors, validated them with other published datasets, and identified an age-related increase in the content of monocyte-derived macrophages that display an M1-like proinflammatory and phagocytic phenotype. Furthermore, the in vitro experiments done by Gather et al. (2022) show that the proximity of fibroblasts isolated from aged skin samples prods the neighbor macrophages toward a more proinflammatory phenotype and that this could be enhanced by exposing them to supernatants of senescent fibroblasts. Cytokines that are commonly associated with aging of, infection of, and damage to the skin such as IL-6, CXCL-1, and TNF-α are expressed in significantly higher quantities by macrophages cocultured with aged fibroblasts. Moreover, this inflammatory phenotype of macrophages could further exacerbate this condition by in turn negatively impacting the transcriptional profile of dermal fibroblasts. These in vitro experiments revealed that fibroblasts, which had contact with proinflammatory macrophages, produce more matrix-degrading proteins such as matrix metalloproteinase 2 and fewer ECM components such as procollagen, thereby possibly contributing to the aging-related decline of the ECM.

These findings provide interesting clues to solve urging open questions on cellular dynamics in skin aging. The foremost of these is on what factors contribute to the age-related decline in the clearance of dermal senescent cells. The failed senescence clearance is observed in tissues presenting chronic inflammation and proteolysis; however how inflammation prevents the elimination of senescent cells is unclear. The results by Gather et al. (2022) indicate that at least in vitro senescent dermal fibroblasts promote an M1 phenotype in the monocyte-derived macrophages and increase their phagocytic capacity. However, whether these changes contribute to the decline of the capacity of the macrophages to eliminate senescent dermal cells needs to be established by functional studies in vivo. It also remains to be determined why skin macrophages change their properties during aging. Are the skin macrophages also undergoing senescence induction and consequently lose the capacity to clear parenchymal senescent cells? Although there is a certain amount of evidence on the senescence-like phenotype of macrophages, for example, of foam cells in

[1]*Department of Dermatology, Medical University of Vienna, Vienna, Austria;* [2]*The Christian Doppler Laboratory for Multimodal Analytical Imaging of Aging and Senescence of the Skin (SKINMAGINE), Medical University of Vienna, Vienna, Austria;* [3]*Ludwig Boltzmann Research Group Senescence and Healing of Wounds, Vienna, Austria;* [4]*Ludwig Boltzmann Institute for Traumatology, The Research Center in Cooperation with AUVA, Vienna, Austria; and* [5]*Austrian Cluster for Tissue Regeneration, Vienna, Austria*

Correspondence: Florian Gruber, Department of Dermatology, Medical University of Vienna, Spitalgasse 23, 1090 Vienna, Austria. E-mail: florian.gruber@meduniwien.ac.at

Clinical Implications

- The numbers of monocyte-derived macrophages (MDMs) are elevated in aged skin.
- Interaction with senescent fibroblasts elicits a proinflammatory, phagocytic, M1-like phenotype in the MDM.
- These M1-like macrophages, in return, elicit an extracellular matrix remodeling phenotype in dermal fibroblasts.

atherosclerotic tissue (Childs et al., 2016), it is unclear whether this process occurs also in skin macrophages. A potential clue is that lipid mediators, which are produced by senescent dermal fibroblasts, inhibit phagocytosis by monocyte-derived macrophages (Narzt et al., 2021).

Finally, the study by Gather et al. (2022) suggests that age-associated changes in the ECM might arise not only from the internal changes in senescent fibroblasts themselves but also be influenced by inflammatory macrophages. In other words, the age-related change in fibroblasts' capacity to produce and remodel ECM can be caused by both cell-internal changes of fibroblasts and the inflammation induced in their environment by the M1 macrophages. It is interesting to speculate that this process resembles changes known in wound healing (Ring et al., 2022) and that the inflammation-induced senescence could represent a form of bystander senescence (da Silva et al., 2019).

These and other questions could be potentially addressed by combinations of single-cell and spatial analysis methods. In addition to the spatial assessment of transcriptome, spatial chemical imaging also might address the questions on the interplay between cell types the plasticity of which is increasingly uncovered and the ECM and its structural and chemical modifications in skin aging.

ORCIDs
Florian Gruber: http://orcid.org/0000-0003-1094-5641
Mikolaj Ogrodnik: http://orcid.org/0000-0003-3137-2037

CONFLICT OF INTEREST
The authors state no conflict of interest.

REFERENCES

Childs BG, Baker DJ, Wijshake T, Conover CA, Campisi J, van Deursen JM. Senescent intimal foam cells are deleterious at all stages of atherosclerosis. Science 2016;354:472–7.

da Silva PFL, Ogrodnik M, Kucheryavenko O, Glibert J, Miwa S, Cameron K, et al. The bystander effect contributes to the accumulation of senescent cells in vivo. Aging Cell 2019;18:e12848.

Gather L, Nath N, Falckenhayn C, Oterino-Sogo S, Bosch T, Wenck H, et al. Macrophages are polarized toward an inflammatory phenotype by their aged microenvironment in the human skin. J Invest Dermatol 2022;142:3136–45.e11.

López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. Cell 2013;153:1194–217.

Narzt MS, Pils V, Kremslehner C, Nagelreiter IM, Schosserer M, Bessonova E, et al. Epilipidomics of senescent dermal fibroblasts identify lysophosphatidylcholines as pleiotropic senescence-Associated Secretory phenotype (SASP) factors. J Invest Dermatol 2021;141:993–1006. e15.

Reynolds G, Vegh P, Fletcher J, Poyner EFM, Stephenson E, Goh I, et al. Developmental cell programs are co-opted in inflammatory skin disease. Science 2021:371.

Ring NAR, Valdivieso K, Grillari J, Redl H, Ogrodnik M. The role of senescence in cellular plasticity: lessons from regeneration and development and implications for age-related diseases. Dev Cell 2022;57:1083–101.

Tigges J, Krutmann J, Fritsche E, Haendeler J, Schaal H, Fischer JW, et al. The hallmarks of fibroblast ageing. Mech Ageing Dev 2014;138:26–44.

Zhao X, Psarianos P, Ghoraie LS, Yip K, Goldstein D, Gilbert R, et al. Metabolic regulation of dermal fibroblasts contributes to skin extracellular matrix homeostasis and fibrosis. Nat Metab 2019;1:147–57.