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PROJECTS FUNDED AT THE UNIVERSITY OF PADUA

CHARTAGING - Charting the token of time: yap/taz transcriptional regulators at the roots of aging

A major challenge in aging research is to distinguish which age-related alterations play a driving role and their interconnections. Aging ultimately implies dysregulated transcription; yet, the identity of signaling cascades and transcription factors that control youthfulness and aging in adult tissues remains poorly understood. Aging also entails maladaptive changes in how cells communicate with each other and their surrounding extracellular matrix (ECM). Senolytics approaches have revealed the role of senescent cells as drivers of aging, leaving however unclear what cell types first become senescent in real tissue and why. Here, we aim to address and connect these fundamental unknowns into an integrative view of aging at an unprecedented spatial, temporal, molecular and mechanistic resolution. As preliminary results, we report that aging requires decreased activity of YAP/TAZ mechanosensors in stromal cells leading to unscheduled activation of cGAS/STING signaling, and that aging may be halted by restoring a youthful YAP/TAZ-cGAS/STING signaling balance. But why do we age then? Building on these findings, our hypothesis is that aging initiates from deterioration of our own “structural frames”: from changes in spatial/contextual signals that cells perceive from the ECM, to altered mechanotransduction and increased fragility of the nuclear envelope leading to cell senescence. These processes are reversible and understanding them may reveal new routes to halt aging. For this we will chart and functionally interrogate a multidimensional atlas of aging biology, delving into the logics of tissue physiology and its progressive degeneration over lifetime, also implementing novel methodologies. Our YAP/TAZ prism offers a unique vantage point to dissect causally relevant extracellular and intracellular mechanisms of youthfulness vs. aging, and opens to the exploration of aging remedies to restore youthful tissue ecosystems by restoring youthful YAP/TAZ activity.

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Department: Molecular Medicine

Coordinator: Università degli Studi di Padova

Total EU Contribution: Euro 2.811.871,00

Call ID: ERC-2022-AdG

Project Duration in months: 60

Find out more: <https://cordis.europa.eu/project/id/101098074>