Internship Proposal

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Project Title:
The influence of CDK1:APC/C-Cdh1:FOXM1 feedback loop strength in the proliferative fitness of neighbour cells: insight into the geroprotective role of the FoxM1 transcription factor

Level:

Master Student

Project Summary:

The aging of the global population is putting a significant strain on healthcare systems as age-related co-morbidities become more prevalent. Understanding the process of aging at molecular and cellular levels is crucial to coming up with comprehensive strategies for health-span extension.

As organisms age, there is a complex interplay between cellular senescence and the loss of proliferative capacity. Cellular senescence, that is, a state of permanent cell cycle arrest, has gained solid evidence for its contribution to the aging process and age-related diseases. At the same time, there is a steady deterioration of stem cells, which are crucial for tissue repair, regeneration, and tissue function [1-3]. So, there is an important interconnection between these two processes that should be explored to tackle age-related decline.

We recently found that aging leads to significant changes in cell cycle dynamics and that the feedback regulation loop between CDK1:APC/C-Cdh1:FOXM1 is a major determinant of loss of proliferative capacity during aging, with low FOXM1 levels and high FZR1/Cdh1 levels leading to limited proliferation of old cells [4]. This is in line with previous work in the host lab that supports the FOXM1 gene as a potential aging reversal factor [5–7]. However, it remains unknown if the feedback loop between CDK1:APC/C-Cdh1:FOXM1 is also modulated by non-cell autonomous mechanisms.

Work to be developed by the student:

This proposal aims to determine the non-cell autonomous effect of CDK1:APC/C-Cdh1:FOXM1 feedback loop in the establishment of a microenvironment that inhibits

proliferation and promotes senescence during aging. Human dermal fibroblasts (HDFs) derived from skin biopsies of young and old healthy individuals (Coriell Biobank) will be used to unveil the paracrine effect conditioned media from young (or aged) cells has in old (or young) counterparts. Long-term live-cell imaging in conditioned elder HDFs expressing FUCCI-sensor[8,9] will be used to assess if the paracrine effect of factors secreted by young cells can restore youthful cell cycle dynamics. The temporal insularity of mitosis will be used as a readout of CDK1:APC/C-Cdh1:FOXM1 feedback loop strength. Moreover, mouse adult fibroblasts (MAFs) collected from WT mice and mice that ubiquitously express a FOXM1 transgene with different ages will be used to examine how FOXM1 and FZR1/Cdh1 levels affect cell cycle slowdown, fitness, and senescence accumulation with aging.
With this project, we will ascertain the non-cell autonomous effect of CDK1:APC/C-Cdh1:FOXM1 feedback loop strength on the proliferative fitness of neighbouring cells and its impact on modulation of a pro-senescent environment. This will provide the proof-of-concept that improved cell cycle dynamics in proliferative cells within a tissue can impact the overall cell population fitness and decelerate senescence accrual.

References:

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and progeroid aging phenotypes and extends healthspan. Nat Aging (2022).

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