Internship Proposal

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Project Title:
Feedback regulation behind age-associated cell cycle slow down as a potential anti-aging target

Level:

Master

Project Summary:

It remains elusive why aged cells slowdown proliferation and become senescent. The host lab disclosed the repression of transcription factor FoxM1 as molecular determinant of mitotic decline and senescence during aging. In an independent study, the co-supervisor found that mitosis (M) is temporally insulated from variability in earlier cell-cycle phases due to the robustness of the positive feedback loop controlling Cdk1-CycB1 activity. Since in aged cells both a mitotic delay and a cell cycle slow down were observed, this raises the QUESTION if the cell cycle dynamics during aging disobeys the temporal insulation of M. Moreover, the co-supervisor found that somatic cells have a post-mitotic period during which they are immune to M. This period can be modulated by the strength of the Cdk1:APC/C-Cdh1 feedback loop (i.e., Cdh1 levels). This brings the QUESTION if higher Cdh1 levels in aged cells account for prolonged post-mitotic refractory period and FoxM1 repression

Work to be developed by the student:

Based in these findings, this project AIMS to: 1) investigate for changes in cell cycle dynamics along aging using different cell cycle biosensors for live-cell imaging of single cells followed by mathematical modelling, thereby providing an original molecular signature of the aged cell cycle. 2) characterise the feedback mechanisms in the aged cell cycle, with particular focus on the Cdk1-CycB1 positive feedback regulation and its crosstalk with APC/C-Cdh1; 3) determine the impact of Cdk1:FoxM1:APC/C-Cdh1 feedback regulation in the increased refractory period to mitosis of aged cells and circumvent senescence during aging.

References:

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LOGARINHO E. (2018) FoxM1 repression during human aging leads to mitotic decline and aneuploidy-driven full senescence. Nature Communications. 9(1):2834:1– 17 doi: 10.1038/s41467-018-05258-6.

ARAUJO AR, Gelens L, Sheriff RSM, Santos SDM. (2016) Positive Feedback Keeps Duration of Mitosis Temporally Insulated from Upstream Cell-Cycle Events. Molecular Cell. 64(2):362–375 doi: 10.1016/j.molcel.2016.09.018.

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