



Life Sciences Seminar

Next-generation human cell reprogramming to study age-related neurodegeneration

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Host: Gaia Novarino

Sporadic Alzheimers Disease (AD) exclusively affects people at old age and represents the overwhelming majority of all AD cases, as genetically defined familial cases are the rare exception. Still, most research on AD has been performed on genetic causes and their directly related pathways, also because we were in lack of models that can reflect complex human genetics, physiology, and age in an appropriate human neuronal context. While patient-specific iPSC-based models represent an attractive solution, iPSC reprogramming results in cellular rejuvenation and thus yields phenotypically young neurons. By contrast, direct conversion of old patient fibroblasts into induced neurons (iNs) preserves endogenous signatures of aging. To control for the involvement of aging in human neuronal models for AD, we took advantage of combining both technologies and generated age-equivalent fibroblast-derived iNs, as well as rejuvenated iPSC-derived neurons from a large cohort of AD patients and controls. In addition to their rejuvenated state, we found that iPSC neurons transcriptionally resemble prenatal developmental stages, while iNs reflect adult-like neuronal stages and show little correlation with the prenatal brain. Thus not surprisingly, only age-equivalent adult-like iNs, but not rejuvenated prenatal-like iPSC neurons, revealed a strong AD patient-specific transcriptome signature, which shows high concordance with previous human post-mortem AD studies, and highlights functional gene categories known to be involved in neurodegeneration. Based on AD patient-specific transcriptional, functional, and epigenetic changes, we found that AD iNs display a more de-differentiated neuronal state than control iNs, which might underlie many of the here and previously observed changes in AD. These data show that iNs represent a unique tool for studying age-related neurodegeneration, and support a view where a partially de-differentiated state of aged cells might permit the loss of the specialized neuronal fitness in AD.

Monday, February 25, 2019 11:30am - 12:30pm

IST Austria Campus Seminar Room, Lab Building East



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