Direct neural reprogramming for modeling human brain aging and neurodegenerative disease.

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Direct neural reprogramming of human fibroblasts into induced neurons (iNs) and induced astrocytes (iAs) provides a powerful human cellular model for studying brain aging and neurodegenerative disease. By bypassing pluripotency and neuroprogenitor stages, these cells retain donor specific genetic, epigenetic and biological aging signatures, making them suitable for disease modeling and for developing cell based bioassays. iNs and iAs can be combined with automated high content imaging, quantitative morphology, autophagy marker analysis, transcriptomics, proteomics, phosphoproteomics, DNA methylation aging clocks and single cell omics. These approaches reveal cell type specific differences in autophagy regulation and define neuronal and glial vulnerabilities associated with aging and disease. They also enable reverse translational studies in which patient derived neural cells are used to examine clinically applied or candidate therapeutics. The Fell HD clinical trial provides an example of how patient derived iNs can be used to study pathways that cannot be directly monitored in the living human brain. Fell HD tested felodipine as an autophagy enhancing intervention in early stage Huntington's disease (HD). We generated iNs from control and Fell HD participant fibroblasts and assessed neuronal morphology, *HTT* expression and subcellular autophagy features. HD-iNs showed reduced neuronal complexity and increased *HTT* expression, while DNA methylation analyses indicated accelerated aging in selected patients. Following felodipine treatment, autophagy enhancement was detectable only in a subset of patient derived neurons, with no obvious adverse cellular effects. Importantly, cellular autophagy phenotypes correlated with patient specific treatment responses observed in the trial. These findings support direct neural reprogramming as an age preserving bridge between human brain aging biology and clinical translation. Patient derived iNs provide an experimentally accessible system for studying autophagy, calcium linked stress pathways and treatment response in neurodegenerative disease.