Dynamics of cellular environments underlying aging and Alzheimer's Disease progression

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The brain has a complex cellular environment, with a tight crosstalk between multiple cell types that is critical for its correct function. Despite extensive research much remains unknown regarding the effect and dynamics of the cellular environment of the brain on the progression of disease, especially in the context of progressive neurodegenerative diseases such as Alzheimer's Disease (AD). I will discuss our insights from profiling the transcriptomes of millions of single cells from mouse models and human brain samples, which enabled us to expose the cellular cascade underlying the progression of AD and highlight specific cells. Specifically, by applying machine learning algorithms to single nucleus and bulk RNA-sequencing data, we built detailed cellular maps of the aging human brain, exposing the vast diversity of cells in the aging brain. We developed new computational approaches to capture cellular environments and follow their dynamics along disease progression. Our analysis associated unique subpopulations of glial cells to early and late stages of AD, and uncovered selective vulnerability of inhibitory neuronal subtypes. Moreover, constructing a manifold of cellular environments across individuals, revealed two trajectories that captured distinct cellular cascades associated with different disease outcomes, one of which captured the progression of AD. These new insights are shaping our understanding of the unique cellular environment of the healthy and Alzheimer's disease brains and its dynamics along the progression of the disease.