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Unraveling shared and unique dysregulated transcriptomic meta-programs in synucleinopathies and Alzheimer's disease

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Synucleinopathies and Alzheimer's disease (AD) present both common and distinct molecular and pathological features, but a comprehensive characterization of these diseases remains elusive. In this study, we identified disease shared stress responses between glial cells and distinct cell type specific transcriptomic features between disease groups. Specifically, we constructed a single-nucleus transcriptome atlas of synucleinopathies and AD, analyzing 3.4 million nuclei from 513 post-mortem human brain tissues. Based on 167 transcriptomic meta-programs obtained from 8 major brain cell types, we elucidated disease shared- and specific meta-programs by investigating usage patterns of the individual programs across each group of patients. Notably, we identified 85 disease-associated meta-programs, including common upregulation of inflammatory responses in microglia across synucleinopathies and AD. We further observed uniquely co-dysregulated stress response meta-programs across multiple glial cells. AD presents co-dysregulation in microglia and oligodendrocyte precursor cells (OPCs), while synucleinopathies demonstrated co-dysregulation of OPCs and vascular cells. Aligning the co-dysregulated meta-programs on spatial transcriptomics using MERFISH demonstrates proximally localized distributions. Our large scale single-cell analyses provides insights into the shared and unique molecular signatures underlying neurodegenerative diseases with distinct pathological mechanism.