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AN INTEGRATIVE MULTI-OMICS FRAMEWORK FOR DECODING MICROGLIAL ECOSYSTEMS IN ALZHEIMER'S DISEASE

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Background: Alzheimer's disease involves complex cellular alterations, yet current methods analyze cell states, signaling, and genetic risk in isolation, preventing systems-level understanding.

Methods: We developed an integrative framework combining quasi-binomial compositional analysis, scDemon [1], LIANA [2], scFates [3], and scDRS [4], applied to 12 integrated snRNA-seq datasets from human entorhinal and prefrontal cortex.

Results: Analysis revealed coordinated cellular alterations with inhibitory neuron depletion and microglia expansion. scDemon identified novel microglial states including a filopedia dynamics module (MYO10/PARVG). Trajectory analysis showed progression from homeostatic (P2RY12-high) to proliferative (APOE, AXL-high) and senescent (CDKN1A-high) states. LIANA implicated RTN4-LINGO1 signaling in impaired neuronal repair, while scDRS mapped disease genetic risk to microglial cells.

Conclusion: Our framework links cellular pathophysiology to genetic etiology, providing a blueprint for identifying therapeutic targets in neurodegenerative disease.

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