Array tomography enables correlative volume electron microscopy and spatial transcriptomics

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Abstract

Volume Electron Microscopy (vEM) provides high-resolution data of target structures and resolves three-dimensional representations of otherwise ambiguous biological geometries. While EM provides high spatial resolution, search processes in volumes of several hundreds of square microns is tedious. Multimodal methods like correlated light and electron microscopy (CLEM) allow to bridge these scale. Among the available vEM techniques, array tomography methods like automated tape collecting ultramicrotomy (ATUM) have proven particularly powerful for targeting specific or rare biological structures as needed for correlation as they enable repetitive and large field of view imaging. Previously, we have applied diverse ATUM-CLEM approaches to reveal ultrastructural correlates of neurodegenerative pathologies. These classic correlation techniques annotate ultrastructural data with one or a few molecular targets. With the advent of spatial transcriptomics (ST), the localization of cells with specific expression profiles covering several thousands of transcripts has become accessible. So far, diverging sample preparation techniques have hindered correlated ultrastructural investigation. Here, we developed STcEM, a method that links spatially-resolved gene expression of single cells with their ultrastructural morphology by integrating ST and ATUM on adjacent tissue sections. With this method we successfully mapped microglial classes according to their transcription profile and ultrastructural morphology in a mouse model of white matter lesion. Our results offer a comprehensive view of the spatial, ultrastructural, and transcriptional reorganization of single cells after brain injury.