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Spatiotemporal mapping of CHI3L1 protein and RNA expression in human post-traumatic brain contusions and other neuropathological scenarios

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Background: Chitinase 3-like protein 1 (CHI3L1) is emerging as a promising biomarker for assessing intracranial lesion burden and predicting prognosis in patients with traumatic brain injury (TBI). Following experimental TBI, Chi3l1 transcripts were detected in reactive astrocytes restricted to the pericontusional cortex. However, the cellular sources of CHI3L1 in response to hemorrhagic contusions in the human brain remain unidentified.

Materials and methods: We examined a comprehensive collection of histologically defined acute and subacute human cerebral contusions with various surgical intervals ranging from 10 hours to 20 days using immunohistochemistry. Histomorphological findings were validated through double immunofluorescence for markers such as Col-1, GFAP, NeuN, MBP, Olig-2, Iba-1, TMEM119, P2RY12, and CD68, along with Fluoro-Jade C histofluorescence staining. Additionally, RNAscope Fluorescent In Situ Hybridization (FISH) technology was employed to examine cell-type-specific gene expression and identify the cellular source of this secreted protein.

Results: CHI3L1 was found at meningeal interfaces, showing significant thickening of the subpial glial plate and perimeningeal astrocytes. Paradoxically, CHI3L1-positive astrocytes were identified in neuroanatomical locations distant from hemorrhagic foci, where numerous eosinophilic ischemic neurons also exhibited CHI3L1 immunoreactivity. After delayed surgical decompressions, CHI3L1 immunostaining extended into white matter tracts and interfascicular oligodendrocytes, and highlighted various phagocytic or activated microglial forms. Consistent with the protein-level distribution, RNA spatial mapping confirmed the presence of the corresponding transcripts across distinct brain cell populations, visualized either as discrete, clustered puncta or as a diffuse, dense cytoplasmic signal.

Conclusions: Given these findings, CHI3L1 should not be regarded exclusively as a reactive astrogliosis marker, due to its broad expression across multiple cell types, including astrocytes, neurons, oligodendrocytes, ependymocytes, leptomeningeal cells, microglia, and blood vessels. This non-selective response underscores the potential for CHI3L1 elevation patterns in biofluids to reflect the overall extent of lesion burden.