Cell adhesion molecules in bidirectional signaling between neurons and astrocytes

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INTRODUCTION: Astrocytes in the normal brain possess a stellate shape, reflecting their immobile and quiescent properties. Alternatively, in neurodegenerative diseases or after injury, astrocytes become reactive and acquire the front-to-rear asymmetry characteristic of migratory cells. Cell migration in vitro has been widely studied in cells stimulated by haptotactic stimuli; however, how neurons modulate the migration of reactive astrocytes is unknown. Additionally, neurons also respond to such cell-cell communication by retracting their dendrites and axons through as yet undefined mechanisms. OBJECTIVES: To study the signaling events triggered in astrocytes and neurons involving the three cell adhesion molecules Thy-1, αvβ3 integrin and Syndecan-4. MATERIALS AND METHODS: Biochemical methods, single-molecule tracking and high-resolution nanoscopy were employed. DISCUSSION AND RESULTS: We found that Thy-1, an abundant neuronal glycoprotein, interacted with αvβ3 integrin and Syndecan-4 in astrocytes, initiating signaling events that lead to cellular responses in both cells. While astroytes increased cell adhesion and migration, neurons stopped neurite growth and retracted them. Signaling cascades in astrocytes downstream of the integrin and Syndecan-4 receptors included Ca2+ release from intracellular stores via IP3R activation, release of ATP via hemichannels, P2X7R activation, influx of extracellular Ca2+, activation of PKCα, RhoA and p160ROCK. Interestingly, neuronal Thy-1 engaged by integrins, induced the recruitment of Thy-1 nanoclusters around the transmembrane protein CBP to initiate Src-dependent signaling events that triggered neurite shortening. Altogether, these results suggest that the engagement of these three cell adhesion receptors induces actin reorganization in both neurons and astrocytes, and while changing astrocyte shape and migratory properties, leads to neurite retraction in neurons. CONCLUSION: The events described here for cells in culture might account for the dramatic morphological changes observed in astrocytes and neurons exposed to a pro-inflammatory environment in vivo. Altogether, these findings suggest that communication mediated by surface receptors on astrocytes and neurons might be responsible for some of the changes these cells undergo in vivo upon brain injury.

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