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## Phagocytosis and synaptic pruning are enhanced in mechanically activated glial cells

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Mechanical forces are constantly exerted on cells and tissues within the human body. In brain tissues, mechanical stresses can lead to complex neuroinflammation events. Among the resident cells, microglia and astrocytes are the first line of defense for preserving the homeostasis of brain tissues. Both microglia and astrocytes play a significant role in mediating the progression of a mechanical damage. Microglia are the primary immune cells of the central nervous system and respond to pathogens and injury by changing their morphology and migrating to the site of injury to destroy pathogens. Classic ways of microglia activation can be triggered by antigen presentation like chemokines, damaged-associated molecular patterns (DAMPs) or pathogen particles. During brain injuries, astrocytes and microglial cells can undergo mechanical deformations, leading to a possible alternative mechanism of activation. However, while the impact of chemical signaling on astrocytes and microglia function has been studied in much detail, the current understanding of mechanical signaling is very limited. To address this challenge, we studied in vitro the role of mechanically injured microglia and compared this to a classical activation way with lipopolysaccharides treatment. BV2 and primary microglial cells were cultivated on elastic membranes and mechanically activated by a rapid single stretch (< 1 sec) in order to mimic *in vivo* condition as we found during a traumatic brain injury (TBI). All experiments were conducted 24 hours post-injury. Our findings indicate that 20% stretch of microglial cells does induce an activation through the increase of IBA1 protein level as well as an increase of actin fluorescence signal. This activation state is found to be simultaneous with the stiffening of BV2 cells as we measure it using a ferule-top nanoindenter. In addition, results of migration show a change in cell behavior suggesting that immune glial cells are mechanosensitive and can adopt an activated state in response to a single mechanical stretch. As it has been demonstrated previously, the nucleus is particularly sensitive to mechanical loading because of its mechanical properties regarding other cell compartment. We showed that DNA double-strand breaks is increased after mechanical injury but not after LPS treatment. Nonetheless, we showed a large increase of phagocytosis activity in mechanically activated cells. To understand the consequences generated by this modulation of phagocytic activity, we introduced the microglial cells in microfluidic chambers allowing the isolation of synaptic connections of a cortical neuronal network. We observed an increase in synaptic markers (PSD95 and synaptophysin) inside mechanically activated microglia. Altogether, these results suggest that mechanical activation of microglial cells during traumatic brain injury could be one of the factors leading to neuroinflammation and synaptic pruning in the hours and days following the lesion. Further analysis of the molecular pathways involved in this activation process could lead to new therapeutic strategy to prevent long-term disabilities after trauma.

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