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Microglia monitor and protect neuronal function via specialized somatic purinergic junctions

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Microglia are the main immune cells in the brain with roles in brain homeostasis and neurological diseases. Mechanisms underlying microglia-neuron communication remain elusive. Here, we identified an interaction site between neuronal cell bodies and microglial processes in mouse and human brain. Somatic microglia-neuron junctions possessed specialized nanoarchitecture optimized for purinergic signaling. Activity of neuronal mitochondria was linked with microglial junction formation, which was induced rapidly in response to neuronal activation and blocked by inhibition of P2Y12 receptors (P2Y12R). Brain injury-induced changes at somatic junctions triggered P2Y12R-dependent microglial neuroprotection, regulating neuronal calcium load and functional connectivity. Thus, microglial processes at these junctions could potentially monitor and protect neuronal functions.

Microglia are the main immunocompetent cells of the nervous system and their role in brain development and maintenance of proper neuronal function throughout life is widely recognized (*1*, *2*). Changes in microglial activity are linked with major human diseases including different forms of neurodegeneration, stroke, epilepsy and psychiatric disorders (*3*, *4*).

Microglia perform dynamic surveillance of their microenvironment via motile microglial processes that constantly interact with neurons (*5*, *6*). However, the molecular mechanisms of bidirectional microglia-neuron communication are unclear. To date, the majority of studies have focused on the interactions between microglial processes and synaptic elements, including axonal boutons and dendritic spines, which have commonly been perceived as the main form of interaction between microglia and neurons (*7*, *8*). However, neurons are extremely polarized cells with a high degree of functional independence concerning metabolism and signal integration in their dendritic and axonal compartments (*9*–*11*). The large-scale structure of neurons (i.e., their cell body and axonal/dendritic branches) in the brain is relatively stable under most conditions. In comparison, small synaptic structures, such as dendritic spines and axonal boutons are often distant from neuronal cell bodies and are highly dynamic. Thus, the interactions between microglia and synapses may not fully explain how microglia are capable of monitoring and influencing the activity of neurons, or how early events of cellular injury in the perisomatic compartment are detected. This may be particularly relevant for the migration and differentiation of neural precursors, cell survival and programmed cell death, adult neurogenesis and the phagocytosis of damaged neuronal cell bodies (*12*–*15*). It is not understood how microglia could monitor neuronal status over years or even decades, and discriminate salvageable neurons from irreversibly injured cells mainly based on changes occurring at distant synaptic structures.

To understand the possible mechanisms of effective communication between microglia and neurons, we tested the