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NEUROIMMUNOLOGY

Brain police

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Microglia have multiple functions in the brain, including synaptic pruning during development, removal of dying neurons and detection of invading pathogenic microorganisms. To perform these functions, microglia continuously monitor the extracellular environment by extending and retracting their processes. The molecular mechanisms that underlie this seemingly random baseline motility are unknown, but here, Madry *et al.* show that tonic activity of the two-pore domain K^+ channel THIK1 (TWIK-related halothane-inhibited K^+ channel) plays a key role in this microglial surveillance. In addition, the highly targeted microglial motility (chemotaxis) that occurs after tissue injury requires microglia-expressed purinergic P2Y12 receptors, but not the accompanying ATP-driven activation of THIK1.

In addition to being activated by P2Y12 receptor signalling, THIK1 is, like many two-pore domain K^+ channels, also tonically active. To investigate the role of the tonic and ATP-evoked THIK1 activity in microglia, the authors blocked THIK1 function either pharmacologically or by gene knock-out (KO) and imaged microglia in brain slices and in vivo by two-photon microscopy. Microglia with blocked THIK1 function showed reduced surveillance and a less complex ramification pattern than their wild-type counterparts, but were still able to perform chemotaxis towards an ATP source. In contrast, pharmacological blockade of P2Y12 receptors prevented microglial chemotaxis but had no effect on microglial surveillance.

These findings suggest that THIK1 K^+ channels are required for maintenance of normal microglial ramification and surveillance, whereas P2Y12 receptors are essential for microglial chemotaxis in response to local increases of ATP due to tissue damage. They furthermore show that microglial surveillance of the brain is regulated by microglial membrane potential, which is controlled by the tonic activity of THIK1. In support of this, microglia with THIK1 knocked out exhibited a strongly depolarized membrane potential and were no longer able to generate an ATP-evoked K^+ current.

When microglia become activated, they produce the cytokine interleukin-1β (IL-1β), a key pro-inflammatory driver in many neurodegenerative diseases. IL-1β production requires assembly of the inflammasome, following priming of microglia by activation of Toll-like receptors with molecules such as lipopolysaccharide (LPS) and lowering of intracellular K^+, which might occur, for example, by ATP-evoked THIK1 activation enabling K^+ efflux . The authors found that application of LPS in the presence of ATP resulted in substantial IL-1β release from microglia, which was blocked by pharmacological inhibition or KO of THIK1. Thus, THIK1 activity is also required for inflammasome assembly and IL-1β release.

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ORIGINAL ARTICLE Madry, C. *et al.* Microglial ramification, surveillance, and interleukin-1β release are regulated by the two-pore domain K^+ channel THIK-1. *Neuron* https://doi.org/10.1016/j.neuron.2017.12.002 (2018)