The Role of P2Y12 in Non-Pathological Microglial Functions during Synaptic Plasticity

Synaptic plasticity is critical for neurodevelopment and proper function of the adult nervous system. Studies show that microglia play critical roles in neurodevelopment, but mechanisms driving these roles are poorly understood. We explored purinergic signaling as a potential mediator between microglia and neurons during synaptic plasticity. Purinergic signaling has been implicated in microglial behavior, but studies focused on inflammatory roles. Non-inflamed microglia highly and selectively express the purinergic receptor, P2Y12, which functions in microglial chemotaxis. We posited that purinergic signaling contributes to the microglial motility underlying synapse surveillance and may be critical for microglial roles in synaptic refinement. Our evidence suggests that P2Y12 disruption prevents ocular dominance shifts indicative of synaptic plasticity. P2Y12 disruption also decreases microglial process complexity, without affecting basal microglial process dynamics. In addition, microglial process dynamics appear to be regulated by arousal with increased surveillance during slow-wave sleep-like states. We find that noradrenergic signaling, contributing to arousal, is sufficient to suppress microglial process dynamics and inhibit microglial P2Y12-mediated roles in synaptic plasticity via microglial β2 adrenergic receptors. These data suggest microglia are active participants in cortical network remodeling in adolescent synaptic plasticity primarily during sleep states. These results not only describe novel neuro-immune interactions in the non-pathological brain, but provoke broader considerations of the importance of sleep in microglial roles during neurodevelopment and in neuropathology.