Cell Competition for Neuron-derived Trophic Factor Controls the Turnover and Lifespan of Microglia

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Microglia are brain-resident macrophages capable of long-term maintenance through self-renewal. Yet the mechanism governing the turnover and lifespan of microglia remains unknown. In zebrafish, microglia arise from two sources, rostral blood island (RBI) and aorta-gonad-mesonephros (AGM). The RBI-derived microglia are born early but have a short lifespan and diminish in adulthood, while the AGM-derived microglia emerge later and are capable of long-term maintenance in adulthood. Here, we show that the attenuation of RBI microglia is due to their less competitiveness for neuron-derived interleukin 34 (Il34) caused by age-dependent decline of colony-stimulating factor-1 receptor a (csf1ra). Alterations of Il34/Csf1ra levels and removal of AGM microglia revamp the proportion and lifespan of RBI microglia. Remarkably, the csf1ra/CSF1R expression in zebrafish AGM-derived microglia and murine adult microglia also undergo age-dependent decline, leading to the elimination of aged microglia. Our study reveals cell competition as a general mechanism controlling the turnover and lifespan of microglia.