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News and Commentary

Microglia rules: insights into micoglial–neuronal signaling

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Activation of microglia, which are the resident, intrinsic arm of the CNS innate immune defense, has long been considered as bystander phenomenon of neuropathology, simply acting as scavenger cells. Considering the enormous capacity of biosynthesis after activation, microglia was then widely confined to detrimental aspects of the immune response culpable of amplification of CNS damage (promoting oxidative burst, expression of proteases, BBB damage).[1] Subsequently, this perspective was opposed by beneficial microglial features such as neuroprotection mediated by a plethora of neurotrophins and glutamate channels (trapping glutamate excess at the synapse, thereby reducing excitatoric injury, 'glutaminergic escape').[2–4]

In addition, activated microglia/macrophages are essential for effective tissue debris removal constituting a prerequisite for efficient remyelinization.[5] Finally, activated microglia/macrophages were reported to alter the nonpermissive nature of the CNS promoting axonal growth,[6] thereby stimulating axonal regeneration.[7,8] This functional dichotomy has been related to local and temporal environmental changes during CNS lesion maturation. This suggested a beneficial or detrimental microglia mode specific for a distinct stimulus.[9,10] Thus, 'activated microglia' is not 'activated microglia' and the elicited functional effect is dependent on its corresponding environment, which is persistently changing during evolution of an acute lesion. This concept has been recently confirmed demonstrating CNS axon regeneration to be sensitive to the time of microglia activation, identifying day 3 after acute injury as most beneficial.[8] However, until now, microglia activation modes can still only be categorized as different activation levels (alert, activated, super-activated). This is opposed by little evidence for a specific microglia activation mode categorized as beneficial or detrimental.

Recent results propose a candidate parameter determining a beneficial or detrimental microglial effect and thereby accounting for the functional microglia dichotomy to rely on the specific sensitivity of the environment to microglia contact (a surface tag/receptor encoded on the neuronal surface). Michel Mallat's group and Isabel Dusart[11] revealed that microglia actively promote cell death of developing Purkinje cells (PC) during early postnatal stages (P3). Furthermore, they propose a mammalian form of 'engulfment-promoted cell death' operated by microglia (Figure 1): if microglia migrates into a perineuronal position, coming into contact with a tagged/receptor bearing neuron, they transfer a death signal to the PC facilitating programmed cell death (Figure 1a). In contrast, if microglia is depleted, PC survival is significantly enhanced (Figure 1a). Their finding is in accord with other results reporting microglia/macrophages contributing to cell death of developing neurons,[12] such as retinal cells.[13] Even neurogenesis in the adult brain is suppressed by activated microglia,[14] suggesting that this mechanism is conserved but prevailingly targeting immature neurons. CNS development is characterized by a high rate of cell turn over and the need to eliminate nonsense cellular connections of immature neurons.

To date, several cascades were identified by which microglia induce neuronal death. All of the putative killing pathways have in common that microglia need to get in close contact with the neuron. This is a classical feature of activated microglia, which migrate towards a perineuronal position,[15] a constellation also attributed to protective properties earlier. Thus, a tag/receptor-mediated mechanism encoded on the neuronal surface is likely to be the essential, determining parameter.

It appears that after the developing neuron switches to a vulnerable state characterized by caspase-3 expression, the formation of a tag/receptor is induced – detectable by microglia. However, a neuron can recover and survive if it avoids contact with microglia (Figure 1a). In contrast, contact with microglia is considered acting as a 'second signal' executing cell death ('engulfment-promoted cell death', Figure 1a). This finding originates from the nematode system[16] and has also been reported in the developing mammalian CNS. Demonstrated to be a highly conserved mechanism, its relevance in the adult CNS under neuropathological conditions, especially neurodegenerative diseases (Figure 1b), appears to be very likely but needs to be further investigated. As a fundamental pathway, it might also mediate cell death for other CNS cell populations under vulnerable conditions (Figure 1c).

Marin-Teva *et al*. highlight the functional significance of neuronal–microglia signaling during CNS development and the need for unraveling mechanisms that govern engulfment behavior. It is worth noting that the insights provided identify a major limitation of immune-mediated therapies to promote neuroprotection because of the encoded tag/receptor on the surface of vulnerable, pre-apoptotic neurons in areas at risk undergoing secondary damage. Another implication of these results is essential to the design of future neurorestorative and neuroconstructive strategies using immature neuronal

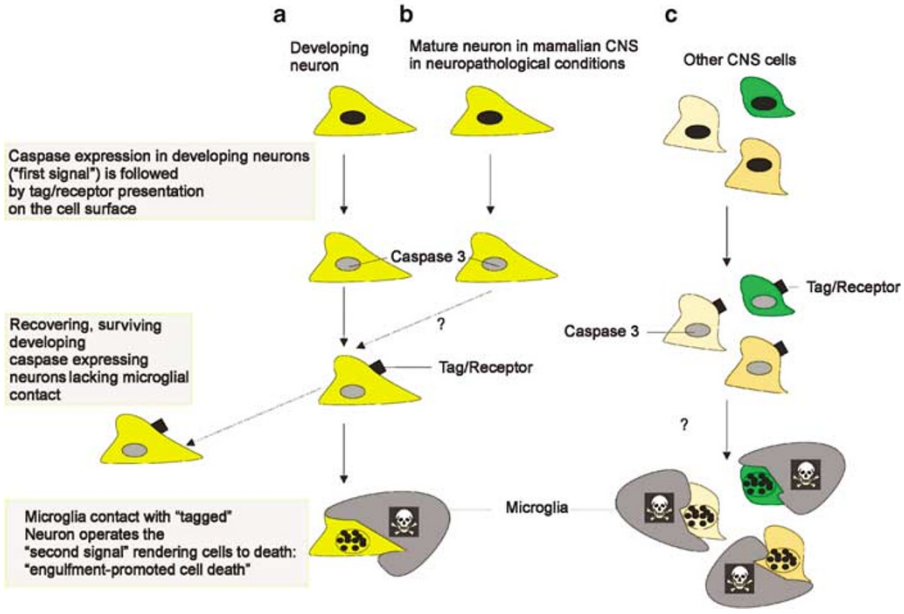

Figure 1 Microglia operated 'engulfment-promoted cell death' is a prominent mechanism during CNS development targeting vulnerable, surface-tagged neurons (**a**). Since it is highly conserved, 'engulfment-promoted cell death' constitutes a candidate mechanism in adult CNS pathology (**b**) (most of which implicate activation of microglia) also targeting non-neuronal cell populations (**c**)

precursor cells (at risk to be hampered by microglia, which is present in virtually every neuropathological condition).

It can be understood from CNS development that the dichotomous microglia contribution after CNS injury might be due to triggering cell death of vulnerable (tagged) neurons as well as promotion of axonal sprouting of surviving (nontagged) neurons.

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1. Banati RB *et al.* (1993) Glia 7: 111–118
2. Gras G *et al.* (2003) Brain Pathol. 13: 211–222
3. Kerschensteiner M *et al.* (1999) J. Exp. Med. 189: 865–870
4. Schwartz M *et al.* (2003) Trends Neurosci. 26: 297–302
5. Friede RL and Bruck W (1993) Adv. Neurol. 59: 327–336
6. David S *et al.* (1990) Neuron 5: 463–469
7. Rapalino O *et al.* (1998) Nat. Med. 4: 814–821
8. Yuqin Y *et al.* (2003) J. Neurosci. 23: 2284–2293
9. Schwartz M (2003) J. Cereb. Blood Flow Metab. 23: 385–394
10. Wyss-Coray T and Mucke L (2002) Neuron 35: 419–432
11. Marin-Teva JL *et al.* (2004) Neuron 41: 535–547
12. Davies AM (2003) EMBO J. 22: 2537–2545
13. Frade JM and Barde YA (1998) Neuron 20: 35–41
14. Ekdahl CT *et al.* (2003) Proc. Natl. Acad. Sci. USA 100: 13632–13637
15. Schwab JM *et al.* (2001) J. Neuroimmunol. 119: 214–222
16. Reddien PW *et al.* (2001) Nature 412: 198–202