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Microglial Control of Neuronal Death and Synaptic Properties

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ABSTRACT
Microglia have long been characterized by their immune function in the nervous system and are still mainly considered in a beneficial versus detrimental dialectic. However a review of literature enables to shed novel lights on microglial function under physiological conditions. It is now relevant to position these cells as full time partners of neuronal function and more specifically of synaptogenesis and developmental apoptosis. Indeed, microglia can actively control neuronal death. It has actually been shown in retina that microglial nerve growth factor (NGF) is necessary for the developmental apoptosis to occur. Similarly, in cerebellum, microglia induces developmental Purkinje cells death through respiratory burst. Furthermore, in spinal cord, microglial TNFα commits motoneurons to a neurotrophic dependent developmental apoptosis. Microglia can also control synaptogenesis. This is suggested by the fact that a mutation in KARAP/DAP12, a key protein of microglial activation impacts synaptic functions in hippocampus, and synapses protein content. In addition it has been now demonstrated that microglial brain-derived neurotrophin factor (BDNF) directly regulates synaptic properties in spinal cord. In conclusion, microglia can control neuronal function under physiological conditions and it is known that neuronal activity reciprocally controls microglial activation. We will discuss the importance of this cross-talk which allows microglia to orchestrate the balance between synaptogenesis and neuronal death occurring during development or injuries.

INTRODUCTION

Microglia are macrophages that are located in the nervous tissue and are able to protect it against infection and injuries through phagocytosis, antigen presentation, and cytokines secretion. This aspect of microglial function has been deeply described (Aloisi, 2001; Kreutzberg, 1996), but a review of literature allows to shed novel lights on this cell type. For instance, during development, microglia invade central nervous tissue at very early stages, before or concomitantly to the neurogenesis (Dalmau et al., 1997), and are able to secrete a wide variety of cytokines that have been implicated in all aspects of neuronal functions (Hanisch, 2002). Therefore, microglia are able to interact with neurons at early stages of differentiation. Indeed, we will discuss the ability of microglia to control developmental apoptosis and synaptogenesis. In the adult, microglia have a relatively high density in neural tissue (Long et al., 1998; Mouton et al., 2002; Orlowski et al., 2003) and form a meshed network able to detect and react to modifications of the local environment (Davalos et al., 2005; Nimmerjahn et al., 2005; Stence et al., 2001). Consequently, most neuronal functions are likely to be regulated by microglia. We will report studies showing that microglia can actively control synaptic functions. This will finally allow to highlight a functional crosstalk between neurons and microglia that set these cells as fulltime partners of neuronal function.

MICROGLIA REGULATE DEVELOPMENTAL NEURONAL DEATH

Microglia are long known for their ability to engulf dead cell bodies (Ferrer et al., 1990; Mallat et al., 2005). This property probably explains why the ability of microglia to kill neurons has been initially investigated. It might also explain the consistent beneficial versus detrimental dialectic of most of the neuron-microglia interactions studies (Ekdahl et al., 2003; Kempermann and Neumann, 2003; Kim and de Vellis, 2005; Taylor and Oppenheim, 2004).

Activated microglia[1] secrete a wide range of factors, some of which can actively trigger apoptosis in neuronal cell cultures: glutamate (Piani et al., 1991) or Tumor Necrosis Factor α (TNFα) with Fas Ligand (FasL) (Piani et al., 1991; Taylor et al., 2005a) in cerebellar granule cells, nitric oxide (NO), and interleukin-1β (IL-1β) in mixed spinal cord cultures (Chao et al., 1992; Tikka and Koistinaho, 2001), cathepsin B in hippocampal and cerebellar granule neurons (Kingham and Pocock, 2001), reactive oxygen species (Colton and Gilbert, 1987) and TNFα with NMDA in neuronal cortex cultures (Floden et al., 2005). At the same time, microglia are also reported to increase neuronal survival through the release of trophic

[1]Activation of macrophages has been extensively and precisely described Taylor et al. (2005b) and shown to be an heterogeneous and complex phenotype. Molecular definitions of microglial activation are still lacking. It is poorly described as stimulation by any kind of factors such as cytokines, growth factors, injuries, inflammation, contact, etc. Considering the complexity of possible stimuli and the probable microglial heterogeneity, it seems obvious that the notion of microglial activation needs further characterization.

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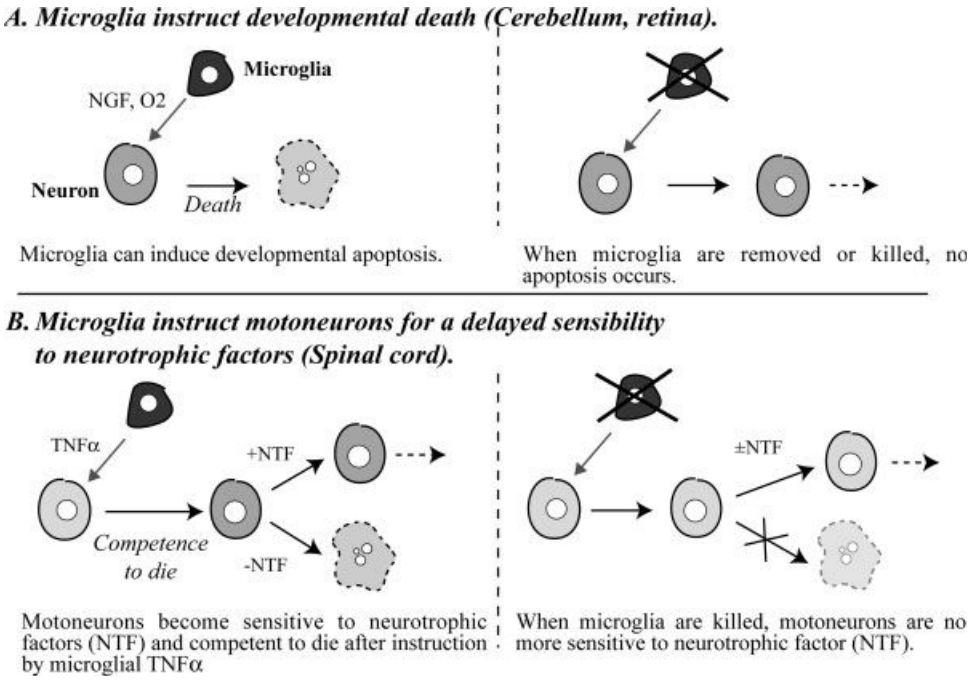

Fig. 1. Microglia control developmental neuronal death. **A**: In retina and cerebellum, microglia are able to actively kill neurons through NGF (retina) or O_2^- (cerebellum). In both cases, when microglia are removed, either by dissection or by selective poisonning, then no neuronal death occurs. **B**: In spinal cord, microglia instruct motoneurons through transient release of TNFα. When microglia are removed, the motoneurons are no more able to die, even in the absence of neurotrophic factor.

and anti-inflammatory factors (Liao et al., 2005; Morgan et al., 2004; Polazzi et al., 2001). These studies indicate the potential of microglia to influence neuronal fate, but have been performed in dissociated cultured cells. In that context, microglia are at least partially activated and these studies can barely be extrapolated to in vivo environments. Studying neurons to microglia interactions in cultured explants allowed to limit this problem. In embryonic chick retina about 50% of the neurons die during the so-called period of programmed cell death (PCD) (Cepko et al., 1996) that temporally follows the invasion of neural tissue by mesoderm derived macrophages. However, the neuronal death is dramatically reduced when embryonic chick retina is dissected out before the invasion of macrophages (Frade and Barde, 1998). It is restored by the addition of microglial cells, and this effect is blocked by Nerve Growth Factor (NGF) antibodies (Frade and Barde, 1998). These results show that NGF produced by macrophages induces developmental neuronal death (Fig. 1A). Such a role of macrophages is not restricted to retina. Using organotypic slices of cerebellum, it was demonstrated that cerebellar microglia also trigger Purkinje cells death (Marin-Teva et al., 2004). When microglia were eliminated from these slices, using liposomes loaded with clodronate, Purkinje cells did not undergo PCD (see Fig. 1A). This effect was shown to be mostly mediated by microglial production of superoxide ions (Marin-Teva et al., 2004). Thus, under more physiological conditions, microglia can induce apoptosis in developing neurons via the release of diffusible factors (Fig. 1). This extends to central nervous system the pioneer work performed on developing eye (Lang and Bishop, 1993; Lobov et al., 2005).

In spinal cord, the relationship is slightly different and microglia induce a delayed competence for motoneurons to undergo apoptosis (Fig. 1B). This again was demonstrated using cultured explants isolated from developing embryos at different stages (Sedel et al., 2004). Indeed, whereas 90% of motoneurons isolated from embryonic day 13 (E13) rat embryos and cultured in explants enter a death program 2 days later, half the motoneurons cultured from E12 embryos escape PCD. This demonstrates that even though motoneurons die around E15, they acquire the competence to die between E12 and E13. It could further be shown that macrophages invading the surrounding somites precisely between E12 and E13 are actually responsible for the acquisition of competence through secretion of TNFα (Sedel et al., 2004). This instruction can be inhibited by killing the macrophages or by blocking TNFα with antibodies, and it is mimicked by exogenous TNFα. Furthermore, motoneurons cell death in explants from either TNF−/− or TNFR1−/− mice is dramatically reduced (see Fig. 1B). Finally, between E12 and E13, microglia and motoneurons transiently express TNFα and TNFα receptor 1 (TNFR1) respectively. These experiments demonstrate that the action of microglia on motoneurons is an instruction to become competent to die rather than a direct induction of apoptosis (Sedel et al., 2004). Importantly, both in spinal cord and in cerebellum, the crosstalk between neurons and microglia occurs during a defined critical period, and microglial ability to induce neuronal death must be triggered (Sedel et al., 2004). The origin of this developmental program remains largely unexplored.

The above described studies show that a common developmental feature of retina, spinal cord, and cerebellum is that microglia invade neural tissue shortly before or concomitantly to the period of naturally occurring neuronal death, and are actively involved in this process. Noteworthy, in these systems the cell death period

precedes the onset of synaptogenesis. Actually, several studies have shown that microglia might also be involved in the regulation of synapses properties.

MICROGLIA REGULATE SYNAPTIC FUNCTION

During cortical development, synaptogenesis occurs during the first weeks of postnatal life reaching a maximum by postnatal day 30 (P30) (De Felipe et al., 1997; Steward and Falk, 1986). Microglia invade the nervous tissue at prenatal stages, but their density displays a significant increase during the first weeks of postnatal life, reaching a maximum by P18 (Dalmau et al., 1998, 2003) that is concomitant to the period of intense synaptogenesis. In addition, at early stages, microglia express thrombospondins (Chamak et al., 1995), a family of extracellular matrix proteins able to induce synaptogenesis (Christopherson et al., 2005) and which absence induces a dramatic reduction in the number of synapses formed during postnatal stages (Christopherson et al., 2005). These observations favor the notion that microglia could somehow regulate developmental synaptogenesis. Involvement of microglia in synaptogenesis can also be deduced from the observation that alteration of developing microglia impacts synaptic properties. Actually, KARAP/DAP12 is a transmembrane polypeptide associated with cell surface receptors which expression is strictly restricted to microglia around birth in the central nervous tissue (Roumier et al., 2004) and which is also found in myeloid and lymphoid cells of the immune system (Tomasello et al., 1998). KARAP/DAP12 mutated mice exhibit an enhancement of hippocampal LTP partly due to a greater permeability to Ca^{2+} of AMPA receptors (AMPARs) (Roumier et al., 2004) and increased sensitivity of NMDAR Excitatory Post-Synaptic Currents (EPSCs) to the NR2B subunit antagonist ifenprodil. Moreover, KARAP/DAP12 mutation induces a specific impairment of synaptic accumulation of the Brain-Derived Neurotrophin Factor (BDNF) tyrosine kinase receptor B (TrkB) suggesting an alteration of the BDNF/TrkB pathway (Roumier et al., 2004). These data provide evidence that the loss of function of a microglial protein expressed during perinatal stages results in alterations in synaptic function and plasticity revealing a developmental interaction between microglia and synaptogenesis.

Microglia express a broad spectrum of cytokines and neurotrophins (Elkabes et al., 1996; Hanisch, 2002) or other diffusible molecules such as glutamate (Barger and Basile, 2001; Floden et al., 2005; Piani et al., 1991) or NO (Chao et al., 1992) which are known to regulate synaptic functions. The regulation of synaptic properties by microglia is thus expected. In some cases, a regulation has been clearly demonstrated. For instance, amyloid peptide (Aβ) is able to impair hippocampal LTP and this inhibition is prevented when microglial activation is blocked by minocycline (Wang et al., 2004). Inhibition of the inducible NO synthase (iNOS) mimics the inhibition of microglial activation, suggesting that NO might be the mediator of this microglia to neuron regulation (Wang et al., 2004). Yet, the involvement of other cell partners has not been ruled out.

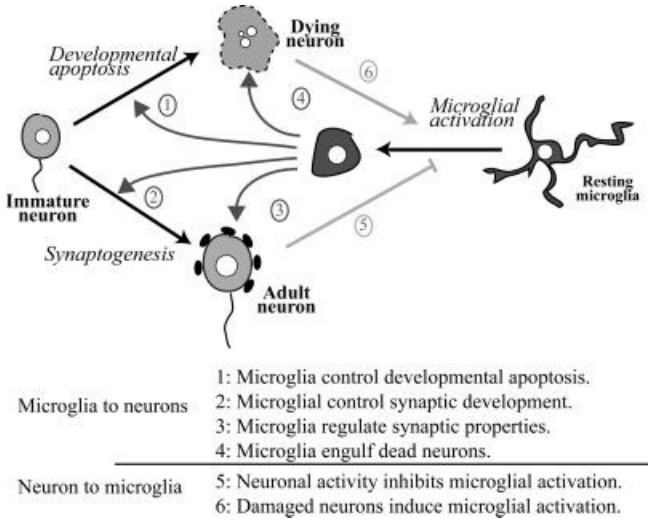

Fig. 2. Functional crosstalks between microglia and neurons. Microglia are able to regulate several aspects of neuronal functions and neurons can control microglial activation.

Microglia express a variety of purinergic receptors, and application of ATP onto cultured microglia triggers the expression of cytokines (Farber and Kettenmann, 2006). It has also been shown that adenosine, which is an ATP metabolite, can coordinate synaptic networks (Pascual et al., 2005). In that case, astrocytes have been identified as the major source of ATP (Pascual et al., 2005), but a similar role of microglia cannot be ruled out. A demonstration of direct ATP signaling between microglia and neurons has recently been given in spinal cord (Coull et al., 2005; Tsuda et al., 2003). In this tissue, ATP stimulation of microglia evokes the release of BDNF which causes allodynia (Coull et al., 2005). This BDNF induces a depolarizing shift in the anion reversal potential in neurons (Coull et al., 2005) which inverts the polarity of currents activated by GABA and converts GABA- and Glycine receptors into activators. These data firmly demonstrate that microglia are able to modulate synaptic activity and highlight BDNF as an intermediate of this modulation.

FUNCTIONAL CROSSTALK BETWEEN NEURONS AND MICROGLIA

The above-described studies demonstrate that microglia are implicated in the control of both neuronal apoptosis and synaptic properties (Fig. 2). Synapses are differentiated regions of adhesion between neurons. It has long been known that cell adhesion and apoptosis are functionally linked (Frisch and Francis, 1994). An attractive hypothesis is now that in central nervous system, microglia orchestrate this regulation. In that model, microglia activated by damaged neurons would instruct locally the nonlesioned or remaining neurons for the delayed formation of new compensatory synapses.

Temporal correlation between microglial activation and apoptosis observed in experimental models of reactive synaptogenesis favors the existence of such mechanism. For instance, kainate seizures induce hippocampal damage with a loss of pyramidal cells in CA1 and CA3 and of interneurons in the hilar region (Yang et al., 1998). In adult, this cell loss is accompanied by neosynaptogenesis after the formation of new recurrent excitatory connections (Nadler et al., 1980a,b; Perez et al., 1996). In young postnatal animals however, no neuronal loss and few if any neosynaptogenesis is observed upon seizure (Yang et al., 1998). Noteworthy, this distinct pattern of synaptogenesis and cell death parallels that of microglial activation. In adults, strong activation of microglia and astrocytes occurs (Rizzi et al., 2003; Rosell et al., 2003) whereas in young animals, few microglial activation can be detected after kainate-induced seizure (Rizzi et al., 2003). Microglial activation associated with neuronal death and followed by synaptogenesis is also observed upon experimental axotomy (Moran and Graeber, 2004). In rodents, facial nerve axotomy induces variable extend of motoneuronal death depending on the age and the species of the animal. In all cases, massive activation of microglia (Graeber et al., 1988) and a deafferentation (synaptic loss) of the motoneurons is observed in the brainstem facial nucleus during the first week postaxotomy (Blinzinger and Kreutzberg, 1968). Several weeks after axotomy, neosynaptogenesis is observed on the soma of the remaining motoneurons (Eleore et al., 2005). Again, the precise role of microglia is not known in the reafferentation process, but it should be noted that upon axotomy activated microglia secrete thrombospondin (Chamak et al., 1995; Moller et al., 1996) which is known to be important for synaptogenesis (Christophersen et al., 2005). This reinforces the hypothesis that upon neuronal death, microglia can instruct remaining neurons for a delayed synaptogenesis.

In these pathological models, damaged or dying neurons induce microglial activation. This highlights the functional interplay between these two cell types, with microglia controlling apoptosis and synaptic properties, and neurons being able to regulate microglial activation. In fact, neuronal control of microglial activation also occurs under physiological situations and might even be a general feature in central nervous tissue. For instance neurotransmitters themselves can modulate microglial activation (Fig. 3). Microglia do express $GABA_B$ receptors which activation strongly decreases the lipopolysaccharide (LPS)-induced secretion of certain but not all inflammatory cytokines (Kuhn et al., 2004). Glycine, which is the other inhibitory neurotransmitter, also attenuates the production of inflammatory cytokines and the phagocytic activity of brain macrophages (Schilling and Eder, 2004). Similarly, noradrenalin reduces the LPS-stimulated release of NO (Chang and Liu, 2000; Farber et al., 2005), IL-6 and TNFα (Farber et al., 2005). Dopamine might also regulate microglial release, but this issue remains debated (Chang and Liu, 2000; Farber et al., 2005). Finally, stimulation of vagus nerve attenuates peripheral macrophage activation through

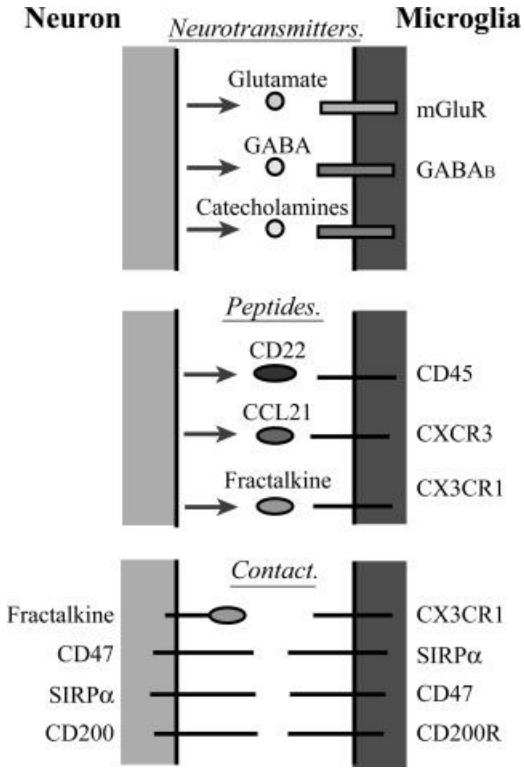

Fig. 3. Molecular actors of neuron to microglia communication. Information flow from neuron to microglia is achieved through contact or by secreted mediators.

the release of acetylcholine (Borovikova et al., 2000; Wang et al., 2003). These observations suggest that neurotransmitters could in general reduce microglial release (Farber et al., 2005). However, the role of glutamate, which is the main excitatory neurotransmitter, remains to be clarified. Indeed, glutamate has been described as a proinflammatory factor acting through both ionotropic and metabotropic receptors (Noda et al., 2000; Tikka and Koistinaho, 2001). But, different glutamate metabotropic receptors might display opposite effects on microglia: group III receptors reduce microglial toxicity (Taylor et al., 2003) whereas group II receptors trigger neurotoxicity (Taylor et al., 2005a). It should now be determined whether and when such regulations occur under normal conditions in the adult CNS.

In organotypic slice cultures, neuronal activity controls the extent of microglial activation since interferon γ (IFNγ)-induced major-histocompatibility complex II (MHCII) expression is increased in microglia when spontaneous neuronal activity is blocked by tetrodotoxin (Neumann et al., 1998). In that case however, the putative intermediate linking neuronal activity to microglial state has not been characterized. In few cases, neuronal factors inhibiting microglial activation could be characterized. In mixed neurons/microglia cultures, neurons secrete CD22 which inhibits proinflammatory cytokines production by microglia through binding to the transmembrane tyrosine phosphatase CD45 (Mott et al., 2004). Similarly, neurons express fractalkine (CX3XL1)

a chemokine that exists in two forms (Bazan et al., 1997), either soluble or anchored to the membrane, and which receptor (CX3CR1) is expressed only by microglia in the CNS (Verge et al., 2004). In cultured microglia, fractalkine is able to downregulate TNFα secretion (Zujovic et al., 2000). In addition, antifractalkine antibodies injected into the ventricle potentiate the LPS induced production of TNFα (Zujovic et al., 2001). Finally, it has recently been shown that loss of CX3CR1 function increases microglial neurotoxicity upon central nervous system alteration (Cardona et al., 2006). This further supports the notion that neuronal fractalkine restraints microglial function.

The existence of a neuronal membrane-anchored fractalkine with a microglial receptor suggests that neuron-microglia crosstalk also takes place by contact. Recent works using transgenic mouse models confirmed the existence of this kind of regulation. Microglia express CD200R, a transmembrane receptor which ligand CD200, a membrane protein with intracellular signaling motifs, is expressed by most of the neurons (Webb and Barclay, 1984). Interestingly, CD200 deletion in mice leads to higher expression of activation markers by microglia as well as proliferation (Hoek et al., 2000). Consequently, various responses to trauma are more severe and more rapid in the absence of CD200. Such a role of CD200-CD200R in the control of microglia by neurons could also be shared by other membrane receptor-ligand systems such as SIRPα-CD47 which are expressed by microglia and neurons respectively, and which mediate inhibitory effects in peripheral macrophages (Barclay et al., 2002; Gordon and Taylor, 2005; Smith et al., 2003).

CONCLUSION

Microglia are a highly responsive population of cells with a well established role in regulating the immune surveillance of the nervous system (Aloisi, 2001; Kreutzberg, 1996; Neumann, 2001). We have now reviewed studies indicating that microglia are also involved in the regulation of various steps of neuronal development such as apoptosis or synaptogenesis. We have not considered the involvement of other non-neuronal cells such as astrocytes or oligodendrocytes, eventhough their interactions are also documented (see for instance (Bezzi et al., 2001) and it is highly probable that other functional interactions are to be understood. Finally, one might anticipate that the real role of microglia in neuronal functions will only be fully understood in light of the elucidation of interplay between microglia, neurons, and the other non-neuronal cells.

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