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A Decade of Diverse Microglial-Neuronal Physical Interactions in the Brain (2008-2018)

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Abstract

Microglia are unique cells of the central nervous system (CNS) with a distinct ontogeny and molecular profile. They are the predominant immune resident cell in the CNS. Recent studies have revealed a diversity of transient and terminal physical interactions between microglia and neurons in the vertebrate brain. In this review, we follow the historical trail of the discovery of these interactions, summarize their notable features, provide implications of these discoveries to CNS function, emphasize emerging themes along the way and peak into the future of what outstanding questions remain to move the field forward.

Keywords

Microglia; Neurons; two photon imaging; physical interactions; P2Y12; NMDAR

1. Introduction: A brief history of microglial-neuronal physical interactions

In vivo imaging opened up new avenues for visualizing brain cells beginning with neurons [19, 22] then astrocytes [40, 59] and more recently microglia [9, 39]. These initial studies have expanded to include the elucidation of microglial phagocytosis in the developing brain and in the neurogenic niche as well as various types of microglial physical contact with neuronal elements. It is now established that microglia interact physically with neuronal somata, axons, axon initial segments and dendrites. In this review, we consider these findings and highlight the field of microglial-neuronal physical interactions as a bona fide area of neuroglial and neuroimmune research.

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Contributions

U.B.E conceived of the manuscript. Both J.O.U and U.B.E wrote and edited the manuscript.

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1.1 Microglial-neuronal physical interactions discovered from 2008-2012

In 2008, Peri and Nusslein-Volhard documented microglial phagocytosis of apoptotic neurons in the developing zebrafish making the zebrafish a powerful system to understand microglial phagocytic mechanisms. In 2009, Wake et al. uncovered transient microglial physical interactions with murine synaptic spines and boutons. In 2010, Tremblay et al. confirmed experience-dependent interactions between microglia and neurons using combined electron microscopic and two-photon imaging approaches. In the same year, Sierra et al. showed that microglia engage in phagocytic clearance of apoptotic neurons in the homeostatic regulation of the neurogenic mouse dentate gyrus. In 2011, Paolicelli et al. first provided experimental support for synaptic elimination by microglia in the developing hippocampus. In 2012, this hypothesis was further developed with the report of complement-dependent synaptic pruning in the mouse visual system. In the same year, two studies in the zebrafish showed further microglial-neuronal physical interactions. First, a novel microglial sensing mechanism for neuronal injury was discovered by Sieger et al. Then, the functional consequence of microglial contact on neuronal excitability was revealed by Li et al.

1.2 Microglial-neuronal physical interactions discovered from 2014-2018

In 2014, back-to-back studies revealed an N-Methyl-D-aspartate (NMDA)R-mediated control of microglial process outgrowth [12, 17]. In 2015, two studies emerged highlighting novel physical interaction . First, Baalman et al. uncovered axon-initial segment (AXIS) microglia. Then, a microglial process convergence phenomenon whereby microglial processes spontaneously focus on neuronal dendrites following epileptiform activity was revealed [14]. In 2016, two fascinating studies from the same lab revealed a neuroprotective targeting of axonal damage in response to excess depolarization [26] and the induction of spines following physical contact with dendritic shafts [33]. In 2017, microglia were shown to interact with dendrites in human epilepsy tissue [66] and in 2018, cerebellar microglia were first observed *in vivo* to dynamically interact with Purkinje neurons [57]. Finally, Weinhard et al. [63] failed to observe microglial phagocytosis of pre- or post-synaptic elements. Rather, more modest remodeling of these elements by microglia was reported. Therefore, a diversity of physical interactions between microglia and neurons haven been documented. These will now be discussed in detail in two categories: transient interactions and terminal interactions.

2. Transient interactions

2.1 Engaging synaptic elements: dendrites, spines and boutons

Wake et al. 2009 [61] first identified synaptic elements as targets of microglial processes. Microglia made contacts with pre-synaptic boutons and post-synaptic spines. Furthermore, contact duration increased about 15-fold in the ischemic penumbra where 25% of contacted boutons were subsequently lost raising the possibility that microglia interact with synapses in a functionally-relevant manner [61]. Later, electron microscopy showed that microglial processes contact only ~3.5% of synapses in the healthy brain [55]. Few (~1.5%) labeled hippocampal spines were contacted briefly (~1.5 mins) by microglial processes [46]. Interestingly, contacts were rarely repeated towards the same spine during an 80-minute

imaging period. Therefore, over time, microglial processes could sample a significant number of synapses. Two-photon imaging and detailed ultrastructural electron microscopy revealed that microglial processes preferentially contacted smaller spines that increased in size following contact. Furthermore, microglial-contacted spines were three times more likely to be eliminated within 48 hours than non-contacted ones. Following sensory deprivation, microglia preferentially contacted larger spines that reduced in size following contact. [60]. Together, these results provide further evidence for putative microglial process regulation of synaptic stability.

The mechanisms underlying microglial-neuronal physical interactions include neuronal NMDAR and microglial P2Y12R signaling [12, 17]. Using mainly pharmacological approaches, these studies showed that neuronal NMDAR activation elicited microglial process outgrowth (where microglial processes radiate outward from their somata in all directions) towards several regions on nearby dendrites and increased microglial process contact of neurons. These responses were recapitulated *during* kainic acid-induced seizures [17]. In addition, a different phenomenon (where microglial processes converged focally to dendritic hotspots, rather than radiating outward on neuronal dendrites) was discovered *following* global glutamatergic activation or kainic acid induced seizures [16]. Both phenomena depend specifically on the GluN2a NMDAR subunit [13]. Knocking out P2Y12Rs abolished both phenomena and corresponded with increased seizure intensities [16, 17] suggesting that these interactions may serve to downregulate neuronal activity.

Long term potentiation (LTP) is thought to be a cellular basis for neuronal plasticity underlying learning and memory [30]. At least two studies combining electrophysiological and imaging approaches have investigated microglial physical responses to high frequency stimulation (HFS) used to trigger LTP. In an initial study, microglial motility was unchanged following LTP [65]. However, a subsequent study examined doubly labelled microglial and neuronal elements at physiological temperatures and showed that following HFS, microglia increased their surveillance density but contacted fewer spines for longer periods of time. NMDARs were required for this increased surveillance [46]. Although the functional significance of these post-HFS contacts are currently unclear, microglia participate in regulating synaptic plasticity [48, 54] and these contacts may thus function to monitor synapses in this context. Microglia have also been implicated in some version of long-term depression (LTD), where synaptic strength is weakened [69].

GluN2a expression and function is upregulated in latter postnatal development. Because NMDAR-triggered microglial process interactions with dendrites require GluN2a function, they are absent in the developing brain. However, microglia still interact physically with neurons in the postnatal brain [33]. In a narrow window between P8 and P10, microglia frequently induced filopodia, precursors to spines, on dendritic shafts in a contact-dependent manner. Moreover, microglial depletion correlated with reduced spine densities and reduced functional synapses suggesting that microglia promote synaptogenesis in the developing cortex [13]. Interestingly, microglia promote learning-dependent synapse formation in adults in a brain derived neurotrophic factor (BDNF)-dependent manner [43]. These findings may imply that microglia employ similar mechanisms during critical synaptogenic periods either in development or during experience-dependent learning.

Microglial physical interactions with neurons also occur in the human brain e.g. in refractory epileptic brain tissue [66]. Here, complement signaling was suggested to be an underlying mechanism for these contacts. Future work will have to assess the extent to which findings in experimental rodent seizures recapitulate these findings of human seizure disorders.

2.2 Engaging with axons and somata

Microglia engage in physical interactions with axons e.g. following repeatedly evoked action potentials in neurons [26]. Here, axons swelled and attracted microglial processes through an ATP-dependent mechanism. This study strongly correlated microglial process contact of swollen axons with a rescue from the evoked hyperactivity. When microglial process contact of axons was blocked, hyperactive neurons failed to be rescued suggesting a paramount neuroprotective role for microglial contact during hyperactivity [26].

Microglia also make contacts with axons in physiology. At least one of such contacts have recently been identified where microglial somata were localized to the axon initial segment of excitatory neurons and are thus termed AXIS (i.e. AXon Initial Segment-associated) microglia [3]. These interactions continually increased from early postnatal development into maturity and are lost in mild traumatic brain injury suggesting relevant homeostatic functions [3]. Other microglia are localized to the neuronal cell body sometimes denoted (perineuronal) “satellite microglia”. Satellite microglia display unique spontaneous electrical activity that is neither displayed by non-satellite microglia nor coupled to their adjacent neuronal partners [64]. Satellite microglia increase in number following microglial activation induced by LPS treatment [8] or axotomy injury [28, 51, 52]. Increased microglial association with neuronal somata in cortical layers III and V reduce inhibitory synapses following LPS treatment [8]. Such LPS treatment and the corresponding elimination of somal inhibitory synapses was neuroprotective in traumatic brain injury [8].

Similar microglial-neuronal interactions were recently reported in the mouse cerebellum [57] and are conserved in the zebrafish. Using *in vivo* two-photon imaging of fluorescently labeled microglia and Ca^{2+}-loaded neuronal somata in the developing zebrafish, [29] showed that microglial processes make repeated contacts with neuronal somata much like in the mouse [60, 61]. Here, localized excitatory neuronal activity was sufficient to attract microglial processes in a purinergic-dependent manner. Upon microglial process contact, neuronal hyperactivity was reduced suggesting once more that microglia function in a neuroprotective homeostatic manner [29]

In closing this consideration of the transient microglial-neuronal physical interactions elucidated to date (**see** Fig. 1), three crucial themes emerge. First, these interactions are intimate involving all structural elements of these cells. Second, these interactions serve mainly neuroprotective functions supporting the hypothesis that microglia participate in the homeostatic regulation of brain physiology. Finally, neuronal NMDAR activation is coupled to microglial P2Y12R signaling indicating that this signaling axis is paramount for regulating microglial-neuronal physical interactions.

3. Terminal interactions

In the brain, excess neurons are produced, many of which are systematically eliminated during development [11, 67]. Microglia are the predominant brain phagocyte during development and disease. Significant progress has been made into documenting and understanding microglial phagocytic clearance of neurons. We will now consider these in the context of development, the neurogenic niche and in the engulfment of viable neurons.

3.1 Phagocytosis in development

Microglia clear dead cells in the developing mouse cortex [2], hippocampus [15, 45, 62] and cerebellum [31]. However, the zebrafish has recently been used to elucidate the underlying mechanisms for microglial phagocytosis. Here, microglia exhibit profound efficiency in the phagocytic clearance of apoptotic debris [44, 58]. Specifically, phosphatidylserine receptors BAI1 and TIM-4 were required for phagosome formation and stabilization, respectively [32], while the v0-ATPase a1 subunit was required for the fusion of phagosomes into lysosomes [44]. Whether these mechanisms are conserved in mammals and/or recapitulated in disease should be a focus of future studies.

3.2 Phagocytosis in the neurogenic niche

After development, new neurons are only generated in the subgranular zone (SGZ) of the hippocampal dentate gyrus (DG) and the subventricular zone (SVZ) along the lateral wall of the ventricle [27]. In the DG, majority of the newborn neurons die by apoptosis following their birth and are efficiently cleared by microglia [53]. Microglial clearance efficiency in the DG is maintained in aging, systemic inflammation and excitotoxic injury but is impaired following seizures and in epilepsy [1, 53]. The proposed mechanism for this impairment involved abolishing purinergic gradients generated by the production of excessive purines following seizures. Since purinergic mechanisms regulate microglial sensing and phagocytic dynamics [6, 18, 35], microglia fail to sense and adequately phagocytose apoptotic cells [1].

Microglia also regulate clearance in the SVZ with great efficiency [20]. Here, the TAM (Tyro3, Axl and Mer) family of receptor tyrosine kinases regulate microglial phagocytosis. However, the functional significance of these interactions also remains to be determined. Interestingly, in a transgenic Parkinson’s Disease (PD) mouse model, TAM proteins were upregulated and correlated with reduced disease survival [20]. Thus, at least in a PD context, microglial phagocytosis aberrantly targeted live neurons (phagoptosis, see below) resulting in poorer outcomes.

3.3 Phagoptosis.

Microglia are also known to induce the killing and subsequent clearance of viable neurons. For example, in the developing cerebellum, microglia induced the demise of Purkinje neurons through the release of superoxide ions [31]. Similarly, apoptosis of hippocampal neurons during development was facilitated by microglial DAP12 and CR3 signaling [62]. Microglial phagocytosis of otherwise viable neurons also occurs during inflammation. Microglia in co-culture with neurons phagocytosed otherwise healthy neurons when exposed to inflammatory agents including amyloid beta. Here, neuronal viability was preserved when

microglial phagocytic processes were inhibited [36, 38]. In this inflammation-induced phagocytosis, microglia triggered the expression of calreticulin on neurons that was subsequently recognized by the microglial low-density lipoprotein receptor-related protein to trigger phagocytosis of otherwise viable neurons. This form of phagocytosis is now referred to as phagoptosis where microglial phagocytosis is the primary inducer of cell death as distinct from traditional phagocytosis where microglial phagocytosis occurs secondary to cell death [4, 5].

3.4 Synaptic pruning

During brain development, extranumerary synapses are eliminated [37, 47] presumably by microglial synaptic pruning. In support of this hypothesis, microglia took up both pre- and post-synaptic material in the developing hippocampus [42]. Fractalkine signaling (CX3CL1-CX3CR1) where CX3CL1 is expressed by neurons and CX3CR1 is solely expressed by microglia in the brain [21, 41] is a unique avenue for microglial-neuronal communications. Mice lacking microglial CX3CR1 exhibited increased synaptic engulfment, transiently reduced spine density and delayed functional neuronal maturation. These aberrations were correlated with a transient reduction in microglial density in CX3CR1-deficient hippocampi [25, 42]. Although these aberrations were restored in adult mice, CX3CR1-deficient mice still exhibited global brain under-connectivity suggesting that transient aberrations in microglial pruning could have long lasting cognitive and social effects [68].

Hoxb8 is also exclusively expressed by a subset of microglia in the brain [7]. Genetic ablation of Hoxb8 resulted in a pathological grooming phenotype in mice reminiscent of obsessive compulsive behavior in humans [7]. These mice exhibit aberrant spine densities compared to wildtype mice [34]. The altered synaptic density in Hoxb8-deficient mice suggests synaptic pruning deficits. Since synaptic pruning is identical in Hoxb8 and non-Hoxb8 microglia [10], these results imply that in the absence of Hoxb8, synaptic pruning by the Hoxb8 microglia is dysregulated.

Microglial complement signaling has also been implicated in synaptic pruning. The first suggestion of complement involvement in synaptic pruning was provided by evidence of C1q upregulation in developing neurons. Furthermore, C1q-deficient mice showed deficient synaptic pruning [56]. Because microglia express C3 receptors (C3R), which are activated downstream of C1q activation, they became a focus of study. Genetic abrogation of C3 or C3R reduced microglial presynaptic engulfment and increased synaptic density [49]. A similar upregulation of C1q, C3 and C3R-dependent microglial synaptic pruning has been reported for glaucoma [56] epilepsy [50, 66] and Alzheimer's Disease [23] indicating that these developmental mechanisms may be re-instituted during neurodegeneration [24].

The above-mentioned studies, while documenting microglial uptake of synaptic material, simply presumed a phagocytic mechanism. However, detailed correlated light and electron microscopy coupled with *ex vivo* imaging was used to test this hypothesis [63]. Remarkably, microglia were not actively engulfing whole synapses. Rather, they refined synapses by partial "nibbling" through a process known as trogocytosis. However, molecular mechanisms underlying the process are not known [63].

In closing this consideration of the terminal interactions employed by microglia to physically interact with neurons (**see** Fig. 2), the zebrafish has been developed as an adequate model to elucidate microglial phagocytic clearance mechanisms during development and novel terminal interactions between microglia and neurons have been discovered including phagoptosis (the phagocytosis of live neurons) and trogocytosis (the refinement of synapses).

4. Concluding Remarks

It has been an exciting decade of research into the transient and terminal physical interactions between microglia and neurons. Three themes emerge from these findings. First, the varied forms of engagement of neuronal elements by microglial somata and processes indicate that microglial-neuronal physical interactions are robust and intimate. Second, with the existence of such interactions in the zebrafish and mouse, these interactions have been conserved across vertebrate species. Finally, these interactions tend to be beneficial. These themes are consistent and when taken in reverse order, it is reasonable that these *beneficial* interactions would be *highly conserved* across species and could thus be expected to *be robust*.

Outstanding questions remain for future research. First, research so far have been mostly descriptive rather than mechanistic. What molecular factors regulate microglial contact-induced filopodia formation in development, AXIS-associated microglial alignment with the axon initial segment, trogocytic refinement of synapses or phagocytic clearance in the neurogenic niche? Moreover, the downstream by which microglia may elicit neuroprotective activity is not known. Second, the functional significance of several of these phenomena are not clear. What is the function of AXIS microglia or of phagocytic clearance in the neurogenic niche? It has been an exciting decade of research on this subject but it has also raised further questions that should be the focus of future research in the next decade.

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HIGHLIGHTS

- Transient microglia-neuronal physical interactions are intimate, homeostatic, and largely dependent on NMDAR activation - microglial P2Y12R coupling.
- Microglia-neuronal interactions could be terminal, for example during phagocytosis and the recently discovered interactions, phagoptosis and trogocytosis.
- Microglia-neuronal physical interactions appear to be beneficial especially the transient interactions, and could be conserved across vertebrate species.

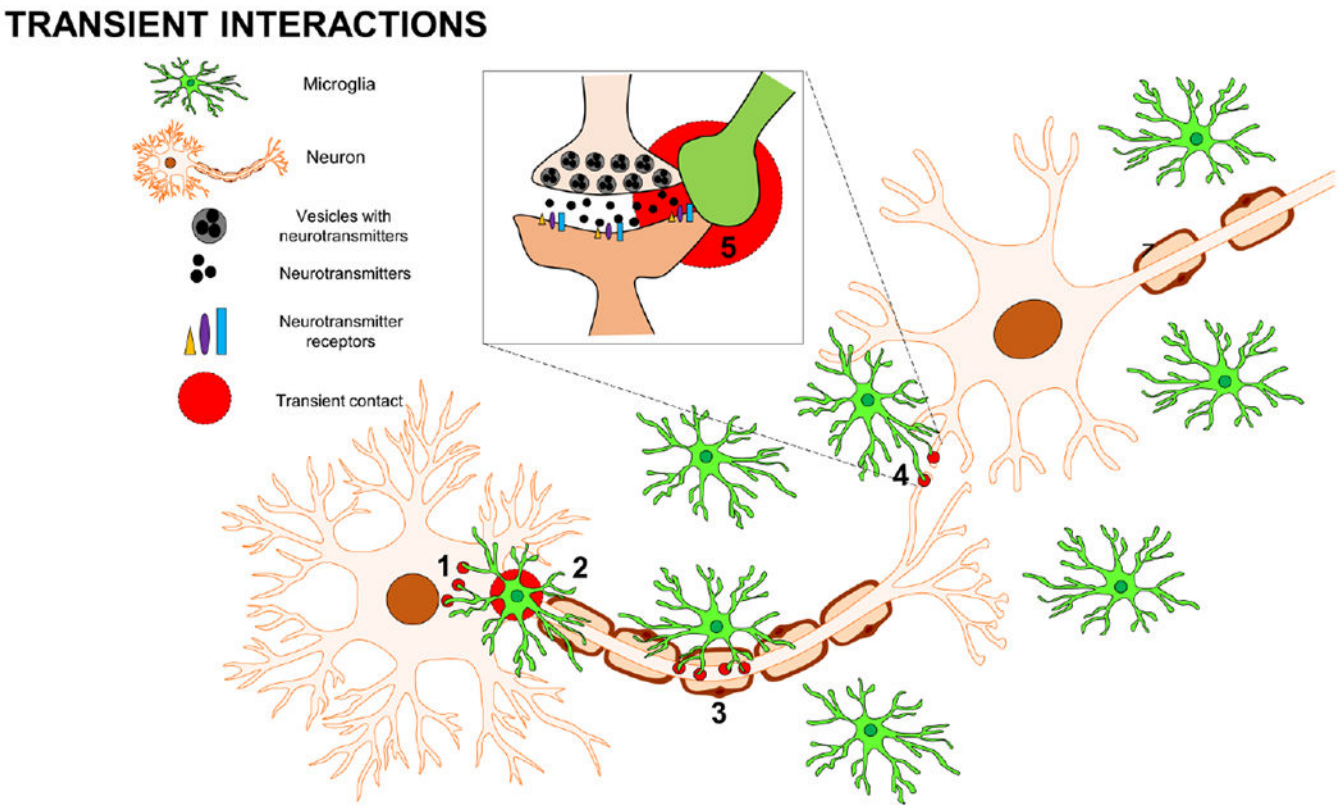

Fig. 1: Transient Microglial-Neuronal Physical Interactions.

Microglia physically interact with neurons in a variety of ways. Some of these interactions are transient and can involve: (1) microglial processes contacting neuronal somata, (2) microglial cell bodies aligning along the axon initial segment (3) microglial processes contacting the neuronal axon, and (4) microglial processes contacting the neuronal synapse including (5) pre- and post-synaptic elements.

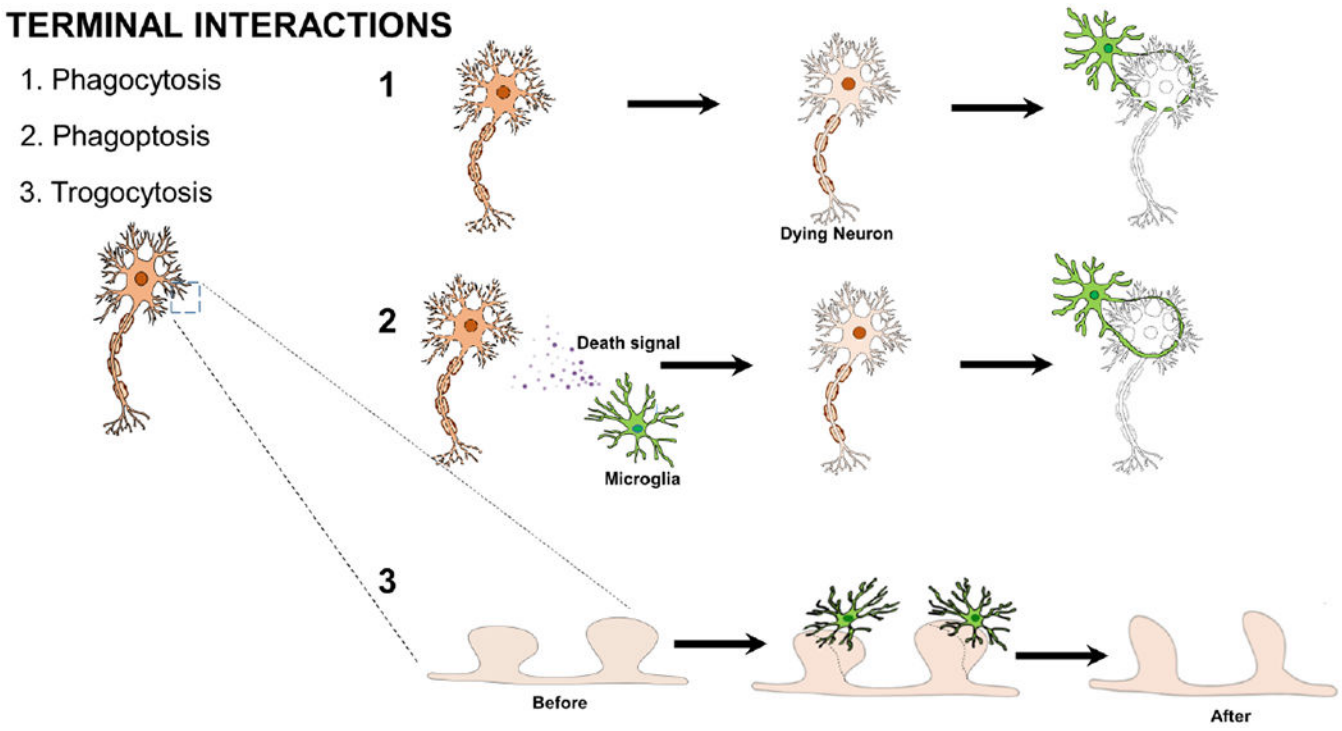

Fig. 2: Terminal Microglial-Neuronal Physical Interactions.

Microglia physically interact with neurons during or in response to the permanent elimination of the neuron or neuronal element. These include: (1) microglial phagocytic clearance of dead neurons during development or in the neurogenic niche; (2) microglial phagoptotic induction of neuronal death and subsequent clearance and (3) microglia trogocytic remodeling of synapses in synaptic pruning.