The role of microglia in synaptic plasticity

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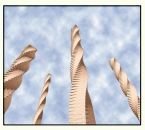


Introduction

In the central nervous system, there are four types of glial cells: astrocytes, oligodendrocytes, polydendrocytes and microglia. They cooperate with neurons, by interacting with synapses and vascular elements, and by providing metabolic and structural support. Concretely, microglial cells have always been seen as an immune cell and, thus, their functions have been confined to response to insults and infections and debris removal. In the last decades, numerous studies have suggested a wider range of roles. Among these roles, microglia were recently involved in the regulation of synaptic plasticity, that is activity-dependent changes in the synaptic strength, as presented in this poster. Therefore, microglial function is critical for the normal functioning of nervous networks and brain physiology.

Methods

Data presented in this poster come from original research papers and reviews published in scientific journals. All the sources used were found in the database PubMed (ww.ncbi.nlm.nih.gov/pubmed) using the following keywords alone or in combination: glia, microglia, synaptic plasticity, LTP, extracellular cell matrix, actin, dendritic spine, imaging studies and neurotransmitters. The relevance of the papers was evaluated according to the novelty and quality of the journal and authors.

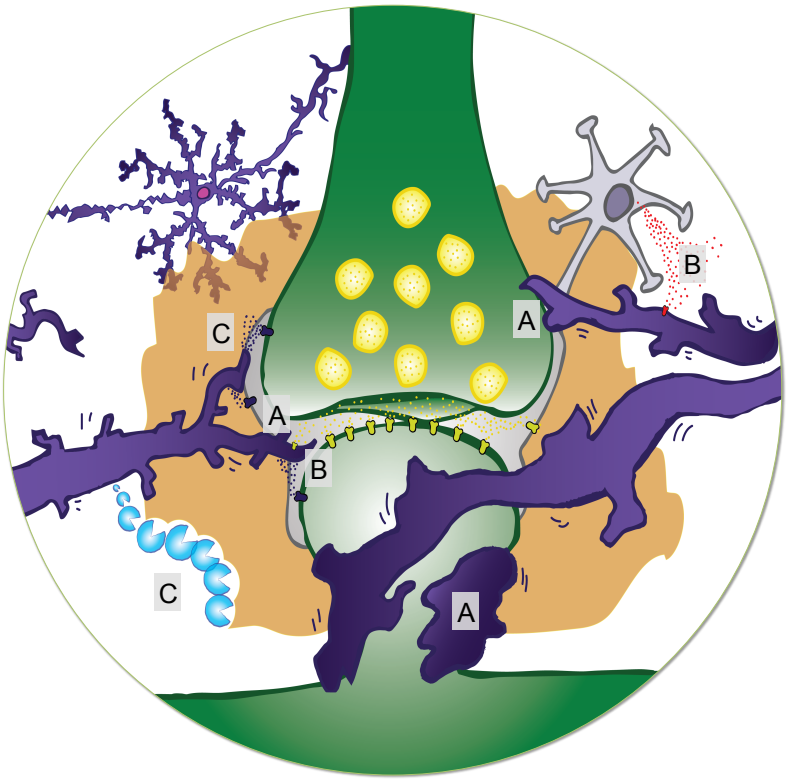
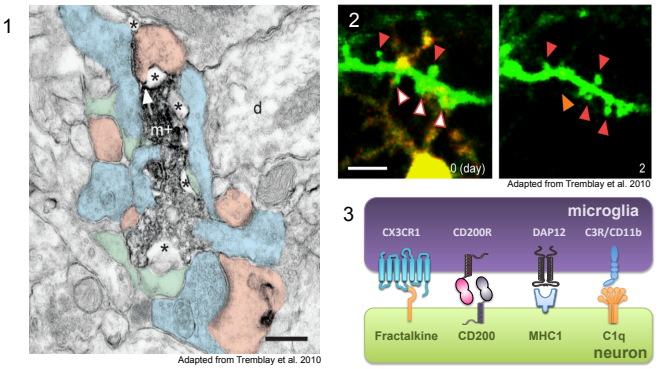


Fig.1. Role of microglia in synaptic plasticity. Purple: microglia. Green: neuronal pre- and postsynaptic terminals. Grey: astrocyte. Orange: extracellular cell matrix. Blue: proteases. Molecules released by microglia (purple), astrocyte (red) and neuron (yellow). Their corresponding receptors have the same colour.

A. Activity-dependent contact and phagocytosis



1. Microglia (m+) contract and extend frequently their processes and establish direct contacts with all the synaptic elements: pre- (blue) and post- (orange) synaptic terminals, astrocytes (green), synaptic cleft (white arrowhead) and perisynaptic extracellular matrix (asterisc).
2. Contacted terminals (white arrowhead) can be phagocytosed (orange arrowhead) dependending on their activity.
3. Direct contacts are mediated by several membrane proteins expressed in both neurons and microglia. These contacts can lead to phagocytosis of the terminal or alterations in the synaptic strength.

B. Receptors expressed in microglia

Microglia can sense their surroundings with the plethora of receptors they express.

Receptor	Effect
β2 (NE,E)	· Reduction of process length and ATP-induced chemotaxis of processes
AMPAR (Glu)	· Increase (and decrease – negative feedback loop) of TNFα release
$P2X_7$ (ATP)	· Release of IL-1β
A2A (adenosine)	· Release of NGF, NO and PGE2

NE: Norepinephrine; E: Epinephrine; ATP: Adenosine triphosphate; AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; Glu: Glutamate; TNFα: Tumor necrosis factor α; IL-1β: Interleukin-1β; NGF: Neuronal Growth Factor; NO: Nitric Oxide; PGE2: Prostaglandin E2

C. Release of soluble substances

Cytokines, neurotransmitters, neuromodulators and trophic factors released by microglia have different effects on neurons and other cells (mainly astrocytes and endothelial cells). Proteases modify the extracellular matrix, several membrane receptors and dendritic spines features.

Molecule	Effect
IL-1β	· Facilitation of NMDAR activation and mediation of LTP-induced increase in dendritic spine size · Induction of trophic factors (IGF-1 and VEGF) release by endothelial cell
TNFα	· Hippocampal synaptic scaling
ATP	· Indirect regulation of glutamatergic transmission. Microglial ATP triggers astrocytic glutamate release, which binds presynaptic mGluR and regulates synaptic plasticity
Glycine	· Enhancement of NMDAR sensitivity and hippocampal LTP
BDNF	· Hippocampal memory consolidation
MMP-9	· Modulation of LTP maintenance: Synaptic NMDAR trafficking, changes in the ECM and dendritic spine size and number

IL: Interleukin; NMDAR: N-methyl-D-aspartate receptor; LTP: Long-term potentiation; IGF-1: Insuline-like growth factor; VEGF: Vascular endothelial growth factor; TNFα: Tumor Necrosis Factor α; ATP: Adenosine triphosphate; mGluR: metabotropic glutamate receptor; BDNF: Brain-derived neurotrophic factor; MMP-9: Matrix Metalloproteinase-9; ECM: Extracellular matrix.

Conclusions

· Resting or ramified microglia is the most dynamic cell in the CNS, since it expands and contracts its processes over seconds to minutes, establishing contacts with synaptic elements with different outcomes, such as synaptic pruning.

· It can monitor the state of synapses directly, by expressing neurotransmitter receptors, or indirectly, via astrocytic signalling.

· Soluble factors released by microglia can modulate the strength of the synaptic transmission and trigger the release of neuroactive substances by other cells.

· Microglial proteases, through modifications of the extracellular matrix and neuronal receptors, exert structural and functional changes in synaptic plasticity.

· Research on the physiology of microglia in healthy scenarios is highly difficult due to the responsiveness of these cells to any experimental procedure.

· New tools are needed for further understanding of their functions in the physiology of the healthy brain.

References

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