Mesenchymal stem cells shape microglia effector functions through the release of CX3CL1

Antonio Uccelli 1 *, Benedetta Parodi 1, Cesare Usai 2, Laura Vergani 3, Simona Casazza 1, Santina Bruzzone 4, Gianluigi Mancardi 1, Debora Giunti 1,

1. Department of Neurology, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI), University of Genoa, Genoa, Italy,
2. Institute of Biophysics, National Research Council, Genoa, Italy,
3. DipTERIS, University of Genoa, Genoa, Italy,
4. Department of Experimental Medicine, Section of Biochemistry, University of Genoa, Genoa, Italy

Objective:

Mesenchymal stem cells (MSC) display a remarkable ability to modulate the immune response and protect the central nervous system (CNS) mainly through the release of soluble factors in a paracrine fashion, affecting the functional behavior of cells in the tissues. Here we investigated the effect of the interaction between MSC and microglia in vitro and we dissected the molecular and cellular mechanisms of this cross talk.

Material and Methods:

In this study we addressed the in vitro effect of MSC on microglia and we dissected the molecular and cellular mechanisms of these interactions demonstrating that MSC can switch microglia from a detrimental behavior dominated by the release of pro-inflammatory molecules to a neuroprotective phenotype associated with the production of anti-inflammatory and trophic factors. Moreover we showed that MSC induce functional changes on microglia as depicted by modifications in intracellular calcium concentration and phagocytic activity. Finally we provided compelling evidence that CX3CL1 released by MSC plays a major role in inducing these beneficial effects on microglia.

Results:

We demonstrated that MSC impair microglia activation by inflammatory cues through the inhibition of the expression and release of inflammatory molecules and stress associated proteins. We showed that MSC significantly increase microglial expression and release of molecules associated with a neuroprotective phenotype such as CX3CR1, NURR1, CD200R and IGF1. Interestingly MSC can enhance functional changes on microglia as depicted by the increase of intracellular calcium concentration and phagocytic activity. This last event is associated with an increased expression of TREM2, an innate immune receptor involved in phagocytosis in the absence of inflammation. The observed effects on CX3CR1-expressing microglia are due to the release of CX3CL1 by MSC, driven by inflammatory signals, as demonstrated by the reversal of the observed results when CX3CL1 expression was silenced in MSC or its release was blocked. Last, we showed that exogenous CX3CL1 induce phenotypic and functional changes of microglia similar to those induced by MSC.

Conclusion:

These findings demonstrate that MSC instruct, through the release of CX3CL1, microglia responsiveness to pro-inflammatory signals by modulating constitutive “calming” receptors, typically expressed by “steady-state microglia” thus switching microglia from a detrimental phenotype to a neuroprotective one.

Keyword:

Mesenchymal stem cells, microglia, chemokines, neuroprotection, immunomodulation.