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The atypical RhoGTPase RhoE/Rnd3 is a key molecule to acquire a in neuroprotective phenotype microglia

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Abstract

Over-activated microglia, the resident immune cells of the brain, play a central role during neuroinflammation, leading to neuronal cell death and neurodegeneration, for example in Alzheimer´s and Parkinson´s disease. Reversion of these over-activated microglia to a neuroprotective phenotype could regenerate a healthy Central Nervous System (CNS)-supporting microglial environment. Our aim was to identify a dataset of intracellular molecules in primary microglia that play a role in the transition of a neurotoxic phenotype to a ramified, neuroprotective one. To do this, we exploited the anti-inflammatory and neuroprotective properties of conditioned medium of adipose-derived mesenchymal stem cells (CM) as a tool to generate the neuroprotective phenotype of microglia in vitro, and we set up a microscopy-based siRNA screen to identify its hits by cell morphology.

We assayed an siRNA array targeting more than 150 genes that codify proteins of cytoskeleton and inflammatory pathways in microglia. From them, siRNA-downregulation of more than 40 genes significantly inhibited the CM-induced transition from a neurotoxic to a neuroprotective microglia phenotype, and 50 siRNA-downregulated genes had the opposite effect. As a proof-of-concept, seven of these targets were validated by downregulation of protein expression with individual siRNAs. They were assayed in functional screens that revealed that the atypical RhoGTPase RhoE/Rnd3 is necessary for BDNF expression and plays an essential role in controlling microglial migration.

Besides the identification of RhoE/Rnd3 as a novel inducer of a neuroprotective phenotype in microglia, we propose a list of potential targets to be further confirmed with selective activators or inhibitors.

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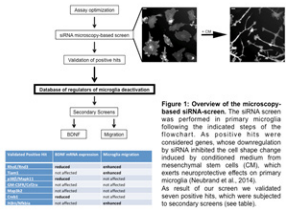

Figure 1: Overview of the microscopy-based siRNA-screen. The siRNA screen was performed in primary microglia following the indicated steps of the flowchart. As positive hits were considered genes, whose downregulation by siRNA inhibited the cell shape change induced by conditioned medium from mesenchymal stem cells (CM), which exerts neuroprotective effects on primary microglia (Neubrand et al., 2014). As result of our screen we validated seven positive hits, which were subjected to secondary screens (see table).

Biography

Veronika Neubrand possesses a Biology degree from the University of Heidelberg and a PhD from the European Molecular Biology Laboratory (EMBL) and the University of Heidelberg, Germany. Currently she holds an associate professorship at the department of Cell Biology at the University of Granada, Spain. In 2009 at the IPBLN-CSIC, Granada, Spain, she started to study the cell biology of microglia, the immune cells of the brain, which play an essential role in neuroinflammation, an important hallmark of neurodegenerative diseases, such as Alzheimer´s and Parkinson´s. In 2014, she was awarded a research grant by the Michael J Fox Foundation, USA. As principle investigator of this grant she identified molecules involved in the generation of CNS-supporting microglia, which represent drug targets for the diseases mentioned above. From 2005 to 2009, Veronika investigated the molecular mechanisms of axonal and dendritic growth in neurons at the Cancer Research UK London Research Institute.

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