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HOT TOPICS

Super glue: emerging roles for non-neuronal brain cells in mental health

William A. Carlezon Jr[1]✉ and Galen Missig[1]

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Accumulating evidence indicates that non-neuronal cells play critical roles in healthy and aberrant brain function. As examples, microglia, astrocytes, and epithelial cells have been implicated in the etiology of psychiatric illness and considered as potential targets for therapeutics [1, 2]. Assimilation of this knowledge has been slow, especially in light of rapid advances in the development of tools that enable precision regulation of neuronal function, but this may reflect the burden of historic (and increasingly archaic) formulations of brain function. Classic conceptualizations of roles for glial cells, in particular, are derived from the knowledge that "glia" comes from the Greek word for "glue"; indeed, it is often assumed that they play passive roles, serving primarily to provide structure for the brain.

As the resident immune cells in the brain, microglia play active roles in critical processes—including neuronal migration, synapse formation and elimination, regulation of neuronal activity, cell death—across the lifespan [1, 3]. They express receptors engendering sensitivity to brain peptides that are involved in stress responsiveness, including CRF (corticotropin-releasing factor) and dynorphin. The corresponding receptors, CRFRs and kappa-opioid receptors (KORs, at which dynorphin acts), regulate release of factors including proinflammatory cytokines, which have been implicated in conditions ranging from mood disorders to Alzheimer's Disease, and BDNF (brain-derived neurotrophic factor), which has been implicated in both the development and relief of depression (Fig. 1). Microglia are located throughout the brain, but interestingly, emerging evidence suggests regional heterogeneity in morphology, function, and gene expression profiles [4]. For example, mRNA encoding KORs (*Oprk1*) in microglia is highest within striatal regions, but appears absent from microglia in other areas (Dropviz.org) [5], raising the possibility that expression is exquisitely responsive to the local milieu. Regardless, considering that BDNF activity in the ventral striatum (nucleus accumbens) appears to promote depressive-like behavior [6], aberrant regulation of microglial BDNF in this region—mediated independently or in combination by CRFRs, KORs, and/or other receptors—is one possible mechanism by which non-neuronal cells can participate in dynamic and persistent changes in neuronal and circuit function that go beyond simply serving as brain connective tissue.

A more comprehensive understanding of how non-neuronal cell types regulate the function of neurons and circuits is needed, particularly in the context of improved use of animal models.

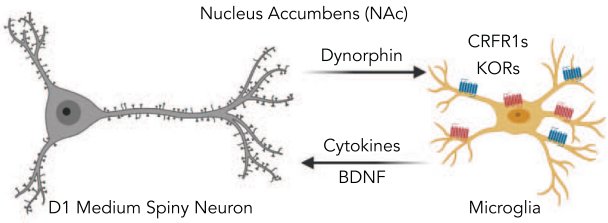

Fig. 1 Simplified schematic of interactions between neurons and microglia in the brain. This example depicts how corticotropin-releasing factor receptors (CRFRs) and kappa-opioid receptors (KORs) expressed on microglia within the nucleus accumbens (NAc) neurons might act independently or in combination to influence the release of proinflammatory and prodepressive factors that act upon neural populations implicated in mood and anxiety disorders.

There have been major technical advances in the use of approaches such as optogenetics, chemogenetics, and organoids to understand how gene-environment interactions affect brain function and as platforms for drug discovery. To date, these approaches focus predominantly on studies of neuronal function, with few examples where complementary approaches are used to investigate the function of non-neuronal cells. Focusing on neurons seems somewhat analogous to the so-called "streetlight effect", where research often occurs under conditions that are most pragmatic, despite interpretational risks. If model systems are to fulfill their maximum potential in the study and treatment of neuropsychiatric illness, methods are needed to ensure that neurons and circuits exist within milieus where all other cell subtypes are present and functioning nominally—or at least remain part of the conversation.

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[1]Basic Neuroscience Division, Department of Psychiatry, Harvard Medical School, McLean Hospital, Belmont, MA, USA. ✉email: bcarlezon@mclean.harvard.edu

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ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to W.A.C.