Correspondence

Microglia, Monocytes, and the Recurrence of Anxiety in Stress-Sensitized Mice

To the Editor:

We read with great interest the article by Weber *et al.* (1) in *Biological Psychiatry* describing the effects of microglia elimination and repopulation on stress sensitization induced by repeated social defeat (RSD). The article highlights brain-immune interactions and, in particular, the importance of stress-primed microglia for monocyte accumulation in the brain of RSD-sensitized mice following acute stress. The transcriptomic analysis of microglia 24 days after RSD could be very useful to other researchers, so the authors may wish to make this information accessible to the community by depositing it to an appropriate data repository.

Several earlier studies by the same group have established robust trafficking of myeloid cells to the brain as a consequence of RSD (2–5). Importantly, the authors have previously reported that transcardial perfusion did not affect the number of Ly6C^{hi} macrophages in the central nervous system after RSD (2). If replicated, this exciting finding would strongly suggest that prolonged stress over a span of several days increases the presence of blood-derived cells either in the perivascular space or in the brain parenchyma (2). At this time, the fate of these engrafted cells in the brain remains to be further elucidated.

In the current study, the authors focus on the effects of a new cycle of acute defeat. They show that the number of CD11b^{+}/CD45^{hi} cells in brain was more than doubled 14 hours after acute defeat in stress-sensitized mice, i.e., mice that had undergone the RSD procedure 24 days previously. Stress-naïve mice subjected to one episode of acute defeat served as controls (1). It should be noted in this context that 14 hours seems like a relatively short period of time for blood-derived cells to engraft the central nervous system, especially as compared with more severe insults with breakdown of the blood-brain barrier such as focal brain ischemia (6). As data on stress-sensitized mice without a new cycle of acute defeat are missing, it is difficult to judge the contribution of previously engrafted CD11b^{+}/CD45^{hi} cells to the increased number of these cells observed here after acute defeat. Again, it would be good if the authors could clarify if brains were perfused.

In line with two earlier reports (7,8), the authors find that the repopulated microglia after treatment with PLX5622 originate from the small number of microglia surviving in the brain (1). However, other studies have yielded strong evidence in support of a key role for circulating monocytes in repopulating the microglial niche (9,10), so the special effects of PLX5622 may not be generalizable to microglia depletion per se. The underlying data obtained by Weber *et al.* (1) from CX$_3$CR1$^{CreER\text{-}YFP}$/R26^{tdTOM} mice also raise a number of issues. First, the authors report that 46% of CD11b^{+}/CD45^{hi} cells isolated from tamoxifen-injected mice after microglial elimination and repopulation lacked yellow fluorescent protein. This lack of yellow fluorescent protein indicates that, at least after treatment with PLX5622, CD11b^{+}/CD45^{hi} cells form a quite heterogeneous population and suggests that the presence of other leukocyte subsets besides macrophages should be investigated (e.g., expression of markers for T cells, natural killer cells, and granulocytes). Second, because of the leakiness of the Cre recombinase acknowledged by the authors, we would rather caution against drawing any firm inferences. In this respect, we also note that additional information from the microglia elimination and repopulation experiment concerning yellow fluorescent protein and tdTOM expression in brain macrophages harvested from CX$_3$CR1$^{CreER\text{-}YFP}$/R26^{tdTOM} mice not treated with tamoxifen would have been very valuable. Finally, and more generally, parameters such as the common CD45$^{hi/lo}$ expression by flow cytometry may conceivably change with injury, treatment, and disease (11,12).

Although blood-derived brain macrophages and resident microglia share many similarities, recent research has highlighted important differences between these two cell types that may be directly relevant to disease outcomes (13–15). By showing that primed microglia and blood-derived cells cooperate to rekindle and augment anxiety, the authors add a new twist to this evolving story. It will be interesting to further delimit the precise roles played by myeloid cells in stress-induced anxiety.

Golo Kronenberg
Ria Uhlemann
Matthias Endres
Karen Gertz

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Article Information

From the University of Leicester and Leicestershire Partnership NHS Trust (GK), Leicester, Leicestershire, United Kingdom; and Charité – Universitätsmedizin Berlin (RU, ME, KG), corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Klinik und Hochschulambulanz für Neurologie und Centrum für Schlaganfallforschung Berlin, Berlin, Germany.

Address correspondence to Karen Gertz, M.D., Klinik und Hochschulambulanz für Neurologie, Abteilung für Experimentelle Neurologie und Centrum für Schlaganfallforschung Berlin, Charité – Universitätsmedizin Berlin, Charitéplatz 1, Berlin 10117, Germany; E-mail: karen.gertz@charite.de.

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