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Commentary Open Access

A Commentary on the Detrimental Effects of Lipopolysaccharide-Induced Neuroinflammation on Adult Hippocampal Neurogenesis Depend on the Duration of the Pro-inflammatory Response

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Commentary

The generation of new neurons is not restricted to embryonic development but continues throughout life in the subgranular zone of the dentate gyrus. The functional integration of adult-born neurons into the hippocampal circuitry confers a unique form of plasticity that contributes to learning and memory processes as well as mood regulation. This neurogenic process is finely modulated by extrinsic factors promoting or inhibiting its progression rate and timing [1].

Neuroinflammation is a hallmark of several pathological conditions underlying neurogenesis dysregulation and deficits on hippocampal-dependent tasks [2]. Therefore, one of the main interests in the neurogenesis field is to understand how neuroinflammation modifies the neurogenic process. Since a pioneering report that used a single systemic LPS administration as a model for inducing brain inflammation [3], it has been well accepted that the inflammatory response sets a non-permissive neurogenic microenvironment in the brain that leads to a reduced number of adult-born neurons. Further studies showed that not only the single exposure of LPS led to a decreased neurogenesis, but expanding previous observations, it has been described a long-term neurogenic decrease associated with chronic neuroinflammation induced by LPS repeated intermittent injections [4]. To what extent is this related to a sustained neuroinflammation response over time? In these and other posterior studies, independently of the LPS administration scheme (single or repeated -consecutive or intermittent), the evaluation of neuroinflammatory-associated neurogenic response has been made shortly after LPS treatment [3-6], when a peak in the brain proinflammatory mediators takes place [7-9]. Thus, the impaired neurogenesis can be associated mainly to the acute proinflammatory response.

New questions arise from the attempts to link neuroinflammation with the decrease in neurogenesis. Does the neuroinflammatory-induced decrease on neurogenesis persist at later time points? Does an LPS repeated intermittent injection induce a greater reduction on neurogenesis if we compare it with a single LPS injection? We addressed these questions in our recent report using previously described LPS protocols (single or four repeated intraperitoneal injections- one per week) but evaluating neuroinflammation-associated parameters seven days after the last LPS challenge and then analyzing the effects of this late neuroinflammatory response on neurogenesis.

Our results showed that both a single and repeated LPS injection induce a systemic inflammatory -associated sickness behavior that is resolved within a week. In contrast, the brain inflammatory response persists 7 days after a single LPS injection, whereas it is not present when the protocol of LPS repeated injections is used. This indicates: 1) that peripheral and central inflammatory responses elapse with different timing accordingly with the type of LPS challenge and 2) LPS intermittent repeated injections induce only an acute neuroinflammatory response [4] pointing out that it may not necessarily induce chronic neuroinflammation since we did not detect a sustained proinflammatory profile at later time points after LPS treatment [10].

Regarding neurogenesis, single LPS administration-induced effects were mainly associated to a decrease in BrdU+/DCX+ cells, suggesting cell proliferation and/or survival dysregulation in this particular cell population. This also shows that the sustained proinflammatory response induced by a single LPS challenge continues impairing neurogenesis. However, after repeated LPS injections this effect is not observed. Considering that we do not observe a proinflammatory profile with the repeated LPS scheme, the detrimental effect of LPS-induced neuroinflammation on neurogenesis seems to be dependent of the presence of a proinflammatory state [10]. Our study is not the first to report that an induced neuroinflammatory response does not necessarily lead to an impaired neurogenesis. For instance, neuroinflammation derived from an adaptative immune response can promote an increase in the neurogenic rate [11]. These findings emphasize the relevance in the combination and timing of the pro- and ant-inflammatory soluble mediators secreted into the neurogenic niche that shape the neuroinflammation-associated neurogenic response.

In relation with the neurogenic process, to the best of our knowledge, we are the first reporting that in physiological conditions almost all proliferating cells are DCX+. Although, this marker is widely used as a post-mitotic immature neuron marker, it is present in committed neuronal progenitors. Thus, our Ki67+/DCX+ data indicate that these type of progenitors (2b and 3) have the highest mitotic activity. This evidence also suggests that type 2a neural progenitors are not as involved in the expansion of the progenitor cell pool as previously thought.

In addition, our work and almost all previous reports, mainly assess the proliferation and/or survival phases of the neurogenic process. Only few studies approach the analysis of the effects of systemic LPS-induced neuroinflammation on other processes associated to neurogenesis, such as the shift in the astrocytic-neuronal differentiation [12] and the maturation of adult-born neurons [13]. Nonetheless, this evidence is also restricted to an acute neuroinflammatory response. What happens as the cells mature under sustained neuroinflammatory conditions? Are these cells able to reach a fully mature phenotype? Which are their functional properties?

Further work must address these questions not just during the acute neuroinflammatory response.

The current evidence establishes that neural precursor cells respond differently to certain stimuli [14-17]. Thus, it also remains to be determined if there are differences in the response of the particular subpopulations of neural progenitors after an inflammatory challenge and what is their contribution to the reduction in the overall number of adult-born neurons. Moreover, it has been shown that LPS administration leads to a proliferative restrain [6]. In line with this observation, our group has reported an impaired cell cycle progression of type 2 progenitors in response to LPS-induced neuroinflammation [18]. Addressing questions regarding proliferative capacity of particular progenitor populations is fundamental to improve our understanding of basic biology of neural precursor cells.

We must keep in mind that neuroinflammation is a physiological response that occurs along impaired neurogenesis and this could prevent the insertion of dysfunctional new neurons born in a non-permissive neurogenic microenvironment. The main research and therapeutic goals should focus on the modulation of the neuroinflammatory response which in turn, would rescue the defective neurogenesis in an appropriate time point.

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