NEUROINFLAMMATION AND ADULT NEUROGENESIS AFTER ACUTE BRAIN INJURY. PERSPECTIVES FOR NEURONAL RECOVERY

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1. Summary

In physiological situations in the adult brain some neural niches (SVZ and DG) have the lifelong ability to produce new neurons. After experimental models of acute brain injury the neurogenic niches increase their proliferation and neuronal differentiation. The physiological relevance of these endogenous neurogenesis as well as the cellular and molecular mechanisms that control the biology of the neurogenic niches in the adult brain are poorly known.

The main objective of the present project is to decipher the functional relevance of the balance between pro- and anti- inflammatory interleukins in the maintenance and differentiation of the adult neurogenic niches in normal and injured brain.
With the present project we described how some inflammatory mediators (IL-10 and IFNγ) have a direct and differential action on the regulation of endogenous neurogenesis in both normal and pathological situations, and they act as relevant tropic factors to modulate the generation of new neurons in the adult brains of experimental animal models.

Moreover, we performed studies on human samples, which suggest that endogenous neurogenesis does not take place in normal and pathological human brain**.**

2. Results

IL-10 levels modulate adult neurogenesis by the activation of specific intracellular pathways

The presence of IL-10 leads to the accumulation of undifferentiated neural progenitor markers (Nestin, Sox1, Sox2, Mash1) and members of the Notch pathway (NICD, Musashi) and keeps progenitors cycling (Ki67, pCDC42). As a consequence, neuronal differentiation is reduced. When IL-10 levels are compromised this gene balance is reversed and neuronal gene expression becomes more prevalent, causing an increase in neurogenesis. (Perez-Asensio et al., 2012; 2013; Pereira et al., 2014).

Moreover, we describe how IL-10 activates STAT3 independently of JAK1 activation, its canonical pathway on the immune system, but dependently on ERK1/2 on SVZ

neuronal progenitors. The pharmacological inhibition of ERK pathway abolished STAT3 phosphorylation and the biological actions exerted by IL-10 on adult SVZ. All together, this indicates that ERK is a mediator of IL-10 action on the adult SVZ.
Molecular studies by lentiviral particles which express a miRNA to inhibit the expression of STAT3 demonstrated that STAT3 is required for IL-10 action on adult neurogenesis. (Pereira et. al., 2015c).

Dual activity of IFNγ on SVZ progenitors by the activation of STAT1

In the present project we deciphered the endogenous actions induced by IFNγ on adult neural progenitors in the normal brain. IFNγ has a dual effect on progenitors by reducing proliferation and promoting neuronal differentiation. However, the antiproliferative action is more intense than the proneurogenic one, and the final outcome is a reduction in endogenous neurogenesis when this cytokine is present. Moreover, we demonstrate that STAT1 is activated and mediates both biological effects promoted by IFNγ on SVZ progenitors mediating (Pereira et al., 2015b).

Actions of IL-10 and IFNγ in combination on the SVZ progenitors

First, we observed that the combination of both cytokines does not affect progenitor viability and the final outcome is comparable to the effects observed for the single presence of IFNγ (see above). This observation suggests that the effects induced by IL-10 are inhibited by the presence of IFNγ. On the other hand, the analysis of intracellular pathway activity determined that the activation of ERK-STAT3 by IL-10 does not apply when IFNγ is present; moreover the Jak2-STAT1 pathway activated by IFNγ is attenuated when IL-10 is present.

Actions of cytokines on animal models of acute brain damage

First, we observed in experimental animal models of acute cerebral lesion (cerebral ischemia and traumatic brain injury) that the magnitude of lesioned area is important for SVZ activity when a lesion occurs. The presence of a large damaged area is needed to get a response from the SVZ.

On experimental cerebral ischemia, we observed by a craniotomy model that cell proliferation on the SVZ is not altered, but a reduction is induced in the number of neuroblasts (DCx+ cells) that exit from the ipsilateral hemisphere to the lesioned cortical regions (Baena et al., 2015). On the other hand, in animal models of traumatic

brain injury we could not detect any alteration on SVZ biology, nor proliferation of neuronal differentiation.

Finally, we analyzed the effects of the IL-10 and STAT1 deficiency in experimental models of cerebral ischemia (craniotomy and intraluminal occlusion). The absence of IL-10 did not induce any additional effect on SVZ proliferation and differentiation, and deficient animals have a similar neurogenesis to IL-10 wild type animals. On the other hand, studies with STAT1 mutant mice demonstrated that this molecule is dispensable for the SVZ endogenous neurogenesis in normal brain situations (Pereira et al. 2015b).

Neurogenesis in human samples

The characteristics of acute brain damage diseases (fast and acute) make it difficult to obtain donors; for that reason the number of human samples compiled and studied in the present project was limited.

Immunofluorescence analysis of brain sections shows that the number of active cells in cycle (KI67+ and PCNA+ cells), as well as the number of neuroblasts (DCX+, PSANCAM+ cells) have a small presence in both normal and lesioned areas in all the analyzed samples; moreover no differences were found in any situation. Additionally, biochemistry studies confirmed that observation, and no significant differences were observed between healthy and lesioned hemispheres by this methodology.

Our studies indicate, similarly to other studies on human samples, that there is no clear evidence of the presence of endogenous neurogenesis in the normal and lesioned adult human brain. In spite of that, these results have scientific value due to the relevance and low availability of analyzed samples in tissue banks.

3. Relevance and implications

When an acute brain lesion take place, a fast progression occurs. In just a few minutes an important loss of cerebral tissue can occur involving an important neuronal cell loss which can cause cerebral functions impairments that might hamper the patients. These neurological diseases are currently the most representative in the Neurology Departments of hospitals, and cause a large health cost in our society.

Moreover, there are no neuroprotective therapies, and the only available treatment, restricted to embolic ictus, is the administration of r-TPA that will dissolve the clot to re-establish blood circulation. Besides, none of the neuroprotective therapies developed in animals models had worked, when translated into clinical application. On the other hand, little is known about the endogenous neuroreparative actions that could be activated from the body to favor the recovery of cerebral functions lost in patients.
The present project points out how inflammatory mediators regulate endogenous neurogenesis. On this basis, pharmacological modulators of this process could be important to modulate tissue regeneration after an acute brain injury. Second, the evaluation and analysis of human samples of acute brain lesions suggest that endogenous neurogenesis is absent in the adult human brain. Though this result is negative, it is relevant in our field of research.

4. Literature Produced

Publications

F. J. Perez-Asensio, U. Perpiñá, A. M. Planas, E. Pozas*
Interleukin-10 regulates progenitor differentiation and modulates neurogenesis in adult brain.
J Cell Sci. 126:4208-19 (2013)

L. Pereira, M. Font-Nieves, C. Van den Haute, V. Baekelandt V, A.M. Planas AM, E. Pozas *
IL-10 regulates adult neurogenesis by modulating ERK and STAT3 activity.
Front Cell Neurosci. 9:57 (2015a)

L. Pereira, R. Medina, M. Baena, A.M. Planas, E. Pozas*
IFN gamma regulates proliferation and neuronal differentiation by STAT1 in adult SVZ niche
Front Cell Neurosci 9:270 (2015b)

M. Baena, I. Pérez-de Puig, E. Martínez, A.M. Planas, E. Pozas*
Neurogenesis in experimental models of acute neuronal injury
Trauma (in press, 2016)

Congress Participations

Pérez-Asensio FJ, Perpiná U, Planas AM, Pozas E[&]

Interleukin-10 modulates neurogenesis on adult SVZ in normal brain

8th FENS (The Federation of European Neuroscience Societies). Barcelona-2012.

Pereira L, Planas AM, Pozas E[&]

Adult neurogenesis and cytokines

The Stem Cell Niche. Copenhagen-2014.

Pereira L, Planas AM, Pozas E[&]

Adult neurogenesis and cytokines

13th CRG Symposium: Gene Regulation, Stem Cell and Cancer. Barcelona-2015c.