



Seminarios internos del IBFG

P53 modulates the inflammatory response in an *in vivo* model of amyloid-beta-induced neurodegeneration

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Salón de actos del IBFG

Oligomerization of amyloid- β ($A\beta$) peptides represents a central event in the etiopathology of Alzheimer's disease. Thus, $A\beta$ oligomers trigger signalling cascades involving alteration of calcium homeostasis, production of reactive oxygen species, inflammatory processes and mitochondrial dysfunction, culminating in neuronal apoptosis. The basic stationary state of microglia is tolerant, pro-homeostatic, and environmental monitoring. Accordingly, to a functional scale, microglial activity can be then categorized into a classical pro-inflammatory and neurotoxic phenotype, known as M1, and the alternative anti-inflammatory M2 phenotype involved in the resolution of inflammation, phagocytosis and tissue repair.

Recently, our group have described a role of p53 in neurodegeneration in an experimental model of $A\beta$ -neurotoxicity. In addition to its traditional functions, p53 has recently emerged as a key modulator of the immune response in microglia. Therefore, we hypothesize that p53 could be modulating the activity profile of the glia in response to $A\beta$ oligomers.

Here we evaluated the function of p53 in the inflammatory response to $A\beta_{25-35}$ oligomers leading to neurodegeneration. To study this, we performed single $A\beta_{25-35}$ (9 nmol) stereotaxic injection in the cerebral right ventricle of mice.

We found that oligomerized $A\beta_{25-35}$ triggered p53 accumulation leading to an early microglial activation. Besides, we found that p53 modulates the M1/M2 activity profile. Moreover, the $A\beta$ injection also increased the number of reactive astrocytes. Altogether, these events lead to dendrite disruption and neuronal death. Furthermore, these effects were prevented by genetic (p53 knockout mice) and pharmacologically (PFT-alpha) inhibition of p53.

Our results highlight a key role of p53 in the $A\beta$ -induced inflammatory response, which may contribute to neurodegeneration.