P53 ORCHESTRATES THE MICROGLIAL RESPONSE UPON AMYLOID-β-INDUCED NEURODEGENERATION *IN VIVO*

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INTRODUCTION

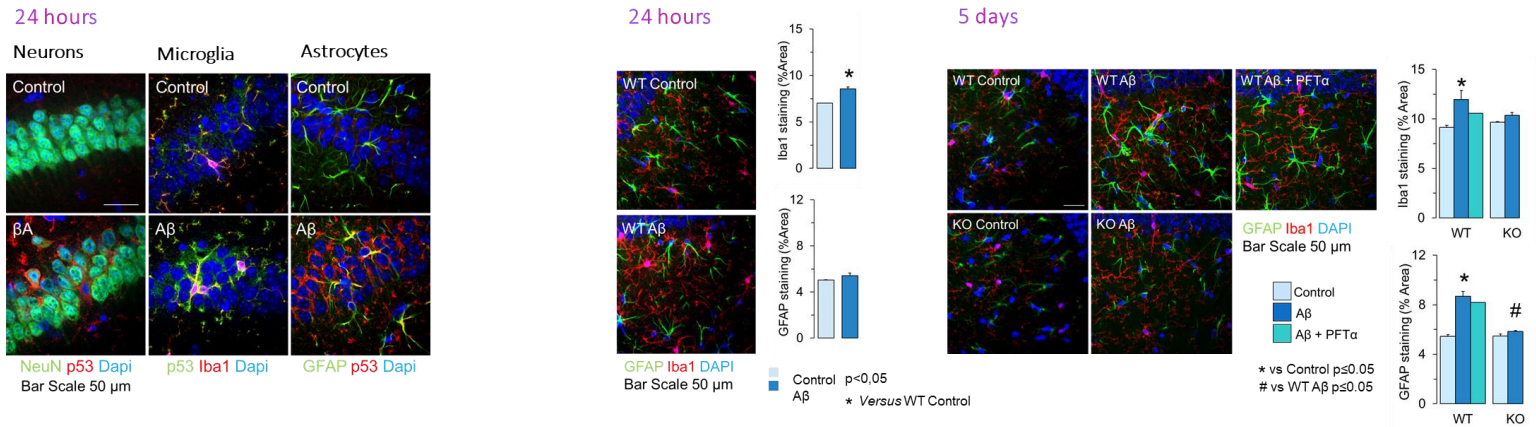
Alzheimer's disease (AD) is a progressive neurodegenerative disorder in which the inflammatory response plays an important role in its development and progression (1). We previously described the key role of p53 in amyloid-β-induced neurodegeneration (2). Moreover, p53 has emerged as a key modulator of the immune response in microglia. Here we evaluate the function of p53 on the microglial response to neurodegeneration caused by Aβ.

MATERIAL AND METHODS

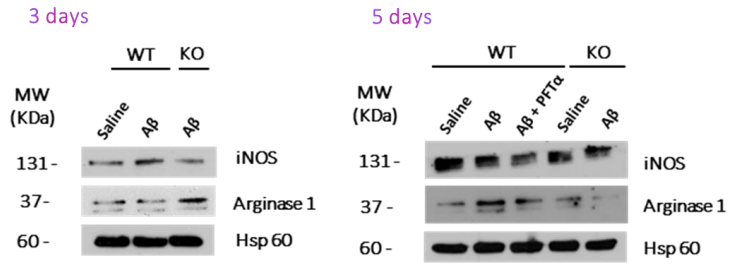
$A\beta_{25-35}$ oligomers were stereotaxically injected in the cerebral right ventricle of *wild-type* (WT) and p53 *knock-out* (KO) mice. In addition, some animals were treated intraperitoneally with the p53 transcriptional activity inhibitor, pifitrin-alpha (PFT-α; 2 $mgKg^{-1}$). Microglial phenotype and neurodegeneration were assessed after injection by western blot and immunofluorescence. The cognitive status of the mice was assessed after injection using the AnyMaze™ system.

RESULTS

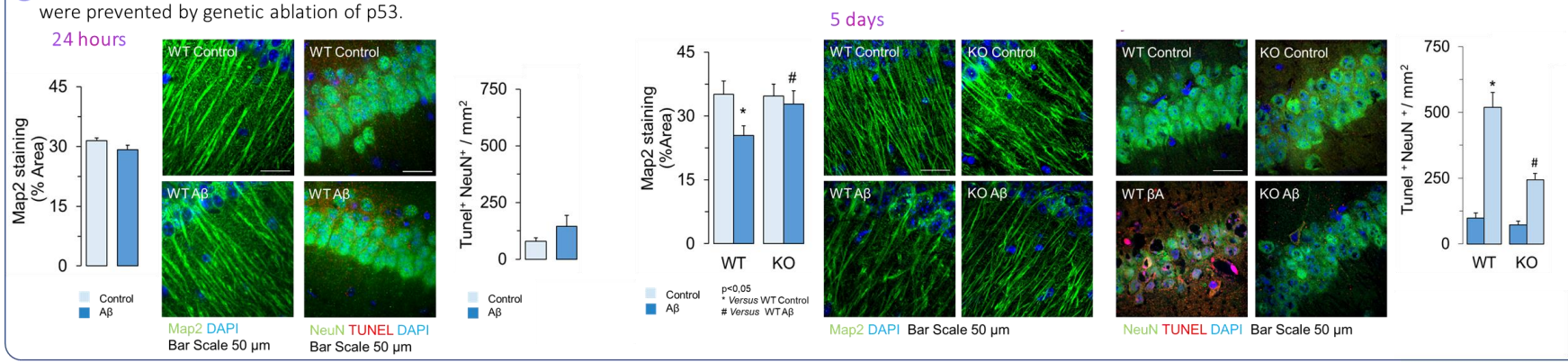
a Aβ triggered p53 accumulation leading to an early microglial activation followed by astrocytic activation. Genetic inhibition of p53 prevented Aβ-induced reactive gliosis in the hippocampal CA1 layer *in vivo*.



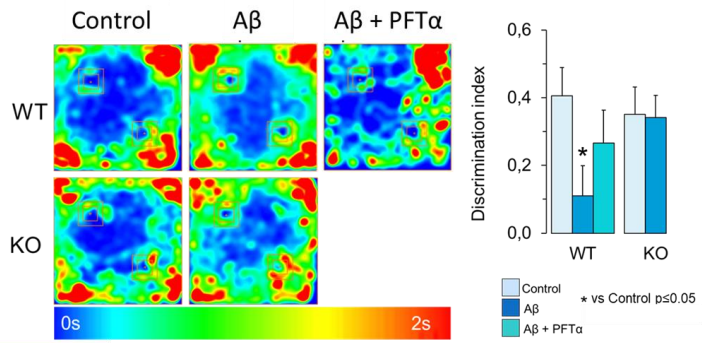
b Aβ promoted, in a p53-dependent manner, an alteration in the abundance of inflammatory mediators in the hippocampus. At 3 days, Aβ promoted the microglial M1 phenotype (increased iNOS and reduced Arginase-1). However, at 5 days, peptide injection induced a microglial M2 phenotype (decreased iNOS and increased Arginase-1). This profile was p53-dependent.



c Aβ promoted dendrite disruption (Map-2 staining) and triggers neuronal apoptosis (TUNEL+NeuN+ cells) in the CA1 hippocampal layer 5 days after peptide injection, which were prevented by genetic ablation of p53.



d Aβ promoted a p53-dependent reduction in memory recognition. As shown in the Novel Object Recognition Test, the cognitive deficit was not observed in neither WT mice treated with PFT-α, nor p53KO mice.



CONCLUSION

Our results demonstrate a key role for p53 in the Aβ-induced inflammatory response, which may contribute to neurodegeneration and cognitive impairment. Therefore, p53 may be useful to develop new therapeutic approaches for Alzheimer's disease.

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