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Tumor necrosis factor-alpha affects human cholinergic neuron development by epigenetic mechanisms

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Loss of basal forebrain cholinergic circuits within the nucleus basalis of Meynert (NBM) is responsible for cognitive deficits in neurodegenerative disorders (ND), such as Alzheimer's disease. Despite the pathogenesis underlying the cholinergic damage is still unclear, growing evidence points to neuroinflammation (NI) as a critical trigger for this process [1]. Here we studied the effects of tumor necrosis factor alpha (TNF-α), the major proinflammatory cytokine involved in NI, in a model of cholinergic neurons from the human fetal NBM (hfNBMs) [2]. Phenotypic characterization, performed by quantitative RT-PCR, flow cytometry and immunocytochemistry analyses, demonstrated that hfNBMs express functional TNF-α receptors and exhibit significant changes upon TNF-α exposure, such as the reduction of immature neuronal markers (nestin, beta-tubulin III), the increase of the mature marker microtubule-associated protein 2 and neurite outgrowth, when compared to untreated cells. Interestingly, TNF-α exposure significantly reduced TrkA, the high affinity nerve growth factor (NGF) receptor, essential for cholinergic neuron survival, while increased p75, the low affinity NGF receptor that mediates apoptotic signals. Given the compelling implication of inflammation-related epigenetic mechanisms in ND we performed a genome-wide methylome analysis of hfNBMs under inflammatory insult. TNF-α exposure for 24-48h altered the methylation pattern of target genes involved in neuronal differentiation and migration. In particular, we observed the promoter hypermethylation of genes involved in neuronal commitment, such as chordin like-1 (CHRDL1) and mesoderm specific transcript (MEST) after 48h stimulation with TNF-α. Accordingly, mRNA expression of both genes was significantly reduced by TNFα treatment. Taken together our results suggest that the TNF-α-mediated inflammatory insult may affect hfNBMs development most likely interfering with the DNA methylation status.

References

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Key words
Neuroinflammation, NGF, DNA methylation.