Autophagy impairment in patients with obstructive sleep apnea mediates intermittent hypoxia-induced oxidative stress and apoptosis via hypermethylation of the *ATG5* gene promoter regions

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Objective: Autophagy is a catabolic process that maintains cellular homeostasis by recycling damaged organelles and acts as a pro-survival mechanism under oxidative stress through inhibiting apoptosis, but little is known about autophagy dysfunction and epigenetic regulation in patients with obstructive sleep apnea (OSA).

Methods: Gene/protein expressions and DNA methylation levels of the autophagy-related genes (ATG) were examined in peripheral blood leukocytes from 64 patients with treatment-naïve OSA and 24 subjects with primary snoring (PS).

Results: LC3B protein expressions of blood monocytes, and ATG5 protein expressions of blood neutrophils were decreased in OSA patients versus PS subjects, particularly in those with depression and daytime fatigue, while p62 protein expression of cytotoxic T cell was increased, particularly in those with nocturia. *ATG5*, *ULK1*, and *BECN1* gene expressions of peripheral blood mononuclear cells were decreased in OSA patients versus PS subjects, while DNA methylation levels of the *LC3B* gene promoter regions were increased, particularly in those with excessive daytime sleepiness. LC3B protein expressions of blood monocytes and DNA methylation levels of the *LC3B* gene promoter region were negatively and positively correlated with apnea hyponea index, respectively. In vitro intermittent hypoxia with re-oxygenation (IHR) exposure to human THP-1/HUVEC cell lines resulted in LC3B/ATG5/ULK1/BECN1 down-regulations and p62 up-regulation along with increased late apoptosis and oxidative stress, while rapamycin (autophagy enhancer) and umbilical cord-mesenchymal stem cell treatment reversed these abnormalities through decreasing DNA methylation levels of the *ATG5* gene promoter region.

Conclusion: Impaired autophagy activity in OSA patients was regulated by aberrant DNA methylation, correlated with clinical phenotypes, and contributed to increased oxidative stress and cell apoptosis. Autophagy enhancers may be novel therapeutics for OSA-related neurocognitive dysfunction.

中文題目：阻塞性睡眠呼吸中止症的細胞自噬作用低下是透過表觀遺傳機制調控

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