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The mechanism of JWA protects dopaminergic neurodegeneration from paraquat in mice

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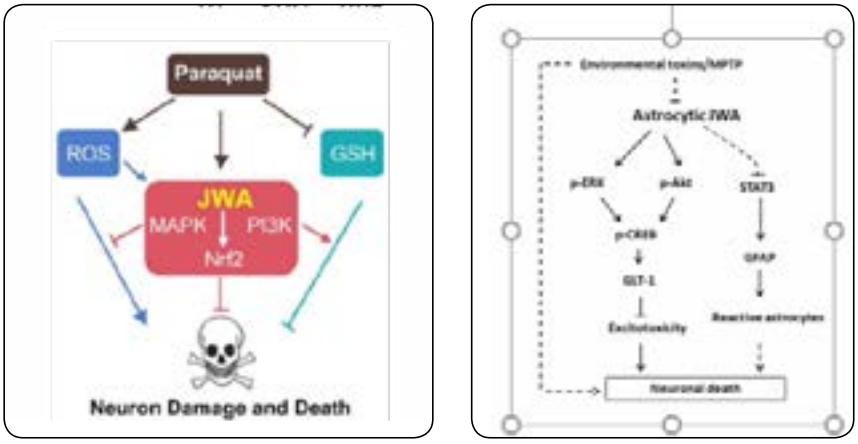
Paraquat (PQ), a widely used environmental toxin in agriculture, contributes to the onset and progression of Parkinson's disease (PD) by damaging the neurons. The JWA gene, also known as ARL6IP5, exhibits the protective effect on dopamine (DA) neuron degeneration. In our study, neuronal and astrocytic JWA knockout (JWA-nKO and JWA CKO) mice were used to exposure of PQ, two neuron cell lines (HT-22, SH-SY5Y) and primary astrocytes were also subjected to PQ treatment. The results showed that PQ administration triggered the upregulation of JWA. Elevated expressions of JWA rescued the redundant abundance of reactive oxygen species (ROS) while increased the levels of glutathione (GSH) and glutathione peroxidase (GPx) under PQ exposure. Astrocytic JWA deficiency repressed expression of excitatory amino acid transporter 2 (GLT-1) and glutamate uptake both in vivo and in vitro. The further mechanistic data indicated that the protective role of JWA in dopaminergic neurons were mainly through anti-oxidative stress induced DNA damage by regulating MEK/PI3K-Nrf2 axis; however it were mediated by MEK/PI3K-GLT1 signaling in astrocytes, through maintaining homeostasis of intracellular excitatory glutamate; and this was confirmed in MPTP/p-induced PD mice model. Taken together, our findings provide novel insights for both neuronal and astrocytic JWA functions in the pathogenesis of neurotoxin mouse models of Parkinson's disease.



A B

Figure 1: The mechanisms of JWA protects dopaminergic neurons from paraquat exposure induced PD like damage. A. in neurons; B in astrocytes.

Recent Publications

1. Wang Q et al. (2017) JWA regulates TRAIL-induced apoptosis via MARCH8-mediated DR4 ubiquitination in cisplatin-resistant gastric cancer cells. Oncogenesis. 6(7):e353.
2. Wang Q et al. (2017) Inhibition of PARP1 activity enhances chemotherapeutic efficiency in cisplatin-resistant gastric cancer cells. Int. J. Biochem. Cell Biol. 92:164-172.
3. Zhao X et al. (2017). JWA antagonizes paraquat-induced neurotoxicity via activation of Nrf2. Toxicol. Lett. 277:32-40.
4. Xu W et al. (2014) JWA reverses cisplatin resistance via the CK2-XRCC1 pathway in human gastric cancer cells. Cell Death Dis. 5:e1551.
5. Miao SH et al. (2014) Astrocytic JWA expression is essential to dopaminergic neuron survival in the pathogenesis of Parkinson's disease. CNS Neurosci. Ther. 20(8):754-62.

Biography

Jianwei Zhou has his expertise in research on DNA damage and repair, cancer initiation, metastasis and drug resistance. Based on the mechanistic discovery of JWA gene in anticancer and neuroprotection, he has developed anticancer polypeptides and small molecular compounds and these will can be potentially used as neurodegenerative protection and cancer metastasis therapeutic agents.

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