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LETTER TO EDITOR

Ferroptosis inhibition: New insights for the treatment of acute lung injury

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Dear Editor,

In recent years, the incidence of acute lung injury (ALI) during clinical treatment has shown a notable upward trend. The aging of the global population, the widespread use of mechanical ventilation, and the emergence of novel pathogens have further exacerbated this situation, posing a severe threat to public health. Consequently, identifying new drug targets and treatment strategies for ALI has become an urgent challenge in the medical field.

Ferroptosis, a distinct form of programmed cell death characterized by iron dependence and lipid peroxidation, differs fundamentally from apoptosis, necrosis, and autophagy, representing a unique mechanism of cell demise.[1] Research indicates that ferroptosis is involved in the occurrence and progression of ALI induced by various factors, such as radiation-induced ALI, ischemia-reperfusion ALI, and lipopolysaccharide (LPS)-induced ALI.[2,3] In a sepsis-induced ALI rat model, abnormal expression of ferroptosis-associated proteins was detected in lung tissues. Notably, pharmacological or genetic inhibition of ferroptosis led to a marked alleviation of ALI symptoms, suggesting that targeted modulation of ferroptosis could be a promising therapeutic approach for ALI.[4,5]

Nuclear factor erythroid 2-related factor 2 (Nrf2) and heme oxygenase-1 (HO-1) play pivotal roles as antioxidant regulators, modulating intracellular iron concentration and metabolism, protecting cells from oxidative stress damage, and inhibiting ferroptosis.[4] The downstream factor solute carrier family 7 member 11 (SLC7A11), a downstream effector of this regulatory network, is recognized for its inhibitory function in ferroptosis. As a key subunit of the cystine/glutamate antiporter system (system xc^-), SLC7A11 facilitates the uptake of extracellular cystine into cells. In addition, glutathione peroxidase 4 (GPX4) is a key protein that inhibits ferroptosis. Regulating certain pathways or directly targeting the activation of Nrf2 can inhibit ferroptosis and reduce lung injury. For example, obacunone can target and activate Nrf2, inhibit the ubiquitination hydrolysis of Nrf2, and improve the antioxidant capacity of lung tissue. Similarly, pachymic acid, glycyrrhizic acid, curcumin, and marmesin regulate different signaling pathways to upregulate the expression of Nrf2, HO-1, GPX4, and SLC7A11 or downregulate the expression of kelch-like ECH-associated protein 1 to reduce ferroptosis levels.

While the concept of ferroptosis is not explicitly defined within the theoretical framework of traditional Chinese medicine (TCM), the application of TCM decoctions has demonstrated beneficial effects of inhibiting ferroptosis in the treatment of ALI. For instance, Huanglian-Jie-du Tang (HLJDD) has been utilized in the management of sepsis-induced ALI, Ganlu Qingwen Fang in LPS-induced ALI, and modified Taoren Chengqi in ventilator-induced lung injury (VILI). Modern pharmacological investigations have revealed that quercetin, a primary monomeric component of HLJDD, exhibits notable

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ferroptosis-inhibitory properties.[6] Ganlu Qingwen Fang has been shown to mitigate inflammatory responses and oxidative stress in rats, thereby conferring protection against ALI, potentially through the modulation of the Nrf2/GPX4 ferroptosis pathway.[7] Modified Taoren Chengqi may ameliorate VILI in rats by activating the Nrf2/GPX4 pathway, consequently inhibiting ferroptosis.[8]

Ferroptosis represents a promising therapeutic target for various pulmonary disorders, including ALI, chronic obstructive pulmonary disease, pulmonary fibrosis, lung infections, and asthma, all of which exhibit ferroptosis during their pathogenesis, thereby influencing the initiation and progression of the diseases.[9] Thus, future investigations should aim to elucidate the specific roles of ferroptosis or crosstalk between different cell death pathways in sepsis-induced ALI and to explore their comprehensive signaling pathways and correlation with disease prognosis. Such research endeavors hold the potential to unveil novel therapeutic targets and strategies for the management of ALI.

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Conflict of interest

The authors declare no competing interests.

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