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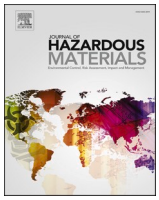

Research Paper

Regulation of H_2S-induced necroptosis and inflammation in broiler bursa of Fabricius by the miR-15b-5p/TGFBR3 axis and the involvement of oxidative stress in this process☆

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ABSTRACT

Hydrogen sulfide (H_2S) is an air pollutant, having toxic effects on immune system. Necroptosis has been discussed as a new form of cell death and plays an important role in inflammation. To investigate the mechanism of H_2S-induced immune injury, and the role of microRNAs (miRNAs) in this process, based on the results of high-throughput sequencing, we selected the most significantly changed miR-15b-5p for subsequent experiments. We further predicted and determined the targeting relationship between miR-15b-5p and TGFBR3 in HD11 through miRDB, Targetscan and dual-luciferase, and found that miR-15b-5p is highly expressed in H_2S-induced necroptosis and inflammation. To understand whether miR-15b-5p/TGFBR3 axis could involve in the process of necroptosis and inflammation, we further revealed that the high expression of miR-15b-5p and the knockdown of TGFBR3 can induce necroptosis. Nec-1 treatment enhanced the survival rate of cells. Notably, H_2S exposure induces oxidative stress and activates the TGF-β pathway, which are collectively regulated by the miR-15b-5p/TGFBR3 axis. Our present study provides a new perspective for necroptosis regulated by the miR-15b-5p/TGFBR3 axis and reveals a new form of inflammation regulation in immune diseases.

1. Introduction

Hydrogen sulfide (H_2S) is a dangerous chemical gas whose toxicity is second only to cyanide. In large poultry farming environments, the decomposition of sulfur-containing organics could produce a large amount of H_2S, thereby injuring poultry health. Several studies have shown that broilers inhaled 20 ppm of H_2S, causing injury to the trachea (Chen et al., 2019; Li et al., 2020), lungs (Wang et al., 2018), jejunum (Zheng et al., 2019), myocardium (Wang et al., 2019), liver (Guo et al., 2019), spleen (Chi et al., 2019), and thymus (Hu et al., 2019), and the mechanisms of injury have been identified, including necroptosis (Li et al., 2020; Chi et al., 2019). Necroptosis is a new form of cell death that can induce cell rupture and release intracellular components that can trigger innate immune responses (Newton and Manning, 2016). Recent studies have revealed the regulation of necroptosis by receptor-interacting protein kinase-1 (RIPK1) and RIPK3, i.e., they may be a mechanism by which necroptosis promotes inflammation. As necroptosis proceeds, phosphorylation events promote the release of proinflammatory cytokines (Newton and Manning, 2016; Pasparakis and Vandenabeele, 2015). Recent researches have revealed key functions of the oxidative stress in necrosis and inflammation. The RIPK3/PGAM5/DRP1 axis can mediate death receptor- and oxidative stress-induced necrosis (Moriwaki et al., 2016). Pressure-induced inflammation and oxidative stress also promotes retinal cells death (Zhao et al., 2015). Bursa of Fabricius is an important lymphoid organ of humoral immunity in birds (Glick, 1983). If it is injured, broilers may develop immunodeficiency-diseases. Therefore, it is important to elucidate the specific mechanism of H_2S-induced bursal immune injury.

Because of the huge role of microRNAs (miRNAs) in cell differentiation, biological development and disease development, and as the key players in the host innate immune response (Maudet et al., 2014), miRNAs has attracted more and more researchers' attention. miRNAs can partially bind to the 3′non-coding regions (3′UTRs) of the target mRNA, and induce protein translation inhibition in an unknown way, thereby inhibiting protein synthesis (Bushati and Cohen, 2007). At present, few studies have reported on how miRNAs regulate necroptotic

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