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Spotlight on Leading Edge Research

Frontline Science: ATF3 is responsible for the inhibition of TNF - α release and the impaired migration of acute ethanol - exposed monocytes and macrophages

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Abstract

Binge drinking represses host innate immunity and leads to a high risk of infection. Acute EtOH - pretreated macrophages exhibit a decreased production of proinflammatory mediators in response to LPS. ATF3 is induced and counter - regulates the LPS/TLR4 inflammatory cascade. Here, we investigated the potential role of ATF3 in LPS tolerance in acute ethanol - pretreated macrophages. We found that there was an inverse correlation between ATF3 and LPS - induced TNF - α production in acute ethanol - pretreated murine monocytes and macrophages. The knockdown of ATF3 attenuated the inhibitory effects of acute ethanol treatment on LPS - induced TNF - α production. Furthermore, ChIP assays and co - IP demonstrated that ATF3, together with HDAC1, negatively modulated the transcription of TNF - α. In binge - drinking mice challenged with LPS, an up - regulation of ATF3 and HDAC1 and a concomitant decrease in TNF - α were observed. Given that HDAC1 was concomitantly induced in acute ethanol - exposed monocytes and macrophages, we used the HDACi TSA or silenced HDAC1 to explore the role of HDAC1 in acute ethanol - treated macrophages. Our results revealed that TSA treatment and HDAC1 knockdown prevented acute ethanol - induced ATF3 expression and the inhibition of TNF - α transcription. These data indicated a dual role for HDAC1 in acute ethanol - induced LPS tolerance. Furthermore, we showed that the induction of ATF3 led to the impaired migration of BM monocytes and macrophages. Overall, we present a novel role for ATF3 in the inhibition of LPS - induced TNF - α and in the impairment of monocyte and macrophage migration.