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Inhibition of gap junctions relieves the hepatotoxicity of TNF-α

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ABSTRACT. The aim of this study was to observe the influence of gap junction (GJ) functional changes on the hepatotoxicity of TNF-α. Three different methods were employed to study functional effects of the GJ inhibition: 1) pretreatment with a GJ inhibitor; 2) inoculation of cells at high and low densities; and 3) inhibition of the expression of connexin 32 (Cx32) by small inhibitory RNA transfection. We then observed the influence of these treatments on hepatotoxicity following treatment with different concentrations of TNF-α for various duration. The hepatotoxicity of TNF-α was observed to occur in a dose- and time-dependent manner; after pretreatment inhibition, the hepatotoxicity of TNF-α was significantly reduced ($P < 0.01$). The hepatotoxicity of TNF-α was also found to be remarkably lower in cells that had been inoculated at low density (as measured by the amount of GJ formation among cells) than in those inoculated at density ($P < 0.01$). In addition, following Cx32 inhibition, the hepatotoxicity of TNF-α was significantly decreased ($P < 0.01$) as well. Together, these results suggest that inhibition of GJ function or of its component Cx32 significantly

decreases the hepatotoxicity of TNF-α, and that the expression of Cx32 plays an important role in the hepatotoxicity of TNF-α.

Key words: Gap junction; TNF-α; BRL-3A cells; Connexin 32; siRNA; Oleamide

