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Treatment with cystamine reduces apoptosis in liver from NZB/W F1 mice

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Abstract

Increased population with hepatic diseases and apoptosis were found in patients with SLE and implicated in the pathogenesis of SLE. Since cystamine has been demonstrated to be beneficial to NZB/W F1 mice in our previous report, this study intends to investigate the effects of cystamine in liver from NZB/W F1 mice. Decreased apoptosis was detected in liver from NZB/W F1 mice given cystamine as compared to those given PBS by TUNEL and caspase-3 activity assay. Fas-dependent apoptotic proteins including Fas, cleaved caspase-8 and tBid were reduced in liver from NZB/W F1 mice given cystamine as compared to those given PBS. Additionally, the mitochondria-dependent apoptotic proteins including cytochrome *c* and Apaf-1 were reduced in liver from NZB/W F1 mice given cystamine as compared to those given PBS. Moreover, increased BCL-2 protein was observed in liver from both mice. Notably, increased NF-κB protein was detected in liver from NZB/W F1 mice given cystamine as compared to those given PBS. These experimental results suggest the effect of cystamine in reducing apoptosis in liver from NZB/W F1 mice through Fas-dependent and mitochondrial-dependent pathways. The phosphorylation of NF-κB (p65) could be a possible mechanism involving anti-apoptotic effects of cystamine in liver from NZB/W F1 mice.

1. Introduction

Systemic lupus erythematosus (SLE) is known as an autoimmune disorder with unknown etiology [1] that impacts various organs including skin, joints, cardiovascular system, nervous system, kidneys and liver [2–7]. However, the underlying pathogenic mechanisms of associated tissues or organs in SLE are still obscure. Recent reports indicated that

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increased population with liver disease was found in patients with SLE [8–10]. A previous study of 19 patients with SLE indicated that 11 patients showed liver abnormality including fatty change, portal tract fibrosis, cellular infiltration, or even cirrhosis [8]. Another study of patients with SLE indicated that 124 of 206 patients tested had at least one abnormal result, and 43 met strict criteria for the existence of liver disease [9]. Although the occurrence of liver disease is not routinely screened, the incidence of hepatic abnormality in patients with SLE was reported as varying from 12% to 55% [10].

Increased Fas and FasL have been implicated in the pathogenesis of SLE [11,12] since the precise role of Fas and FasL in the pathogenesis of SLE is still unclear. Recently, Fas and FasL, the apoptosis-associated molecules, have been implicated in liver damage in patients with SLE by causing liver dysfunction and apoptosis [6,7]. Fas (CD95/Apo-1) is a TNF-receptor alike type 1 membrane protein with a molecular weight of 45–48 kDa [13] and known to be associated with apoptosis in various cells [14]. Moreover, growing evidences and consensus exist that impaired functions of macrophages in clearance for dying cells are contributed to the accumulation of apoptotic cells in tissues of SLE patients [15–17]. Therefore, these findings indicated that persistence of apoptosis and impaired clearance of apoptotic cells in liver is intimate with the pathogenesis of SLE.

Cystamine is known to be an inhibitor of transglutaminase 2 (TG2) by interfering TG2 activity [18,19]. Cystamine is also reported to inhibit caspase-3 activity and indicated in preventing apoptosis [20,21]. Additionally, cystamine has been demonstrated as playing important roles in neuroprotection [22] and prolonged survival and decreased abnormal movements in a transgenic model of Huntington disease [23]. Notably, our recent experimental results demonstrated the beneficial effects of cystamine in reducing MMP-9 activity, TNF-α and TGF-β mRNA expression in macrophage from NZB/W F1 mice and generation of anti-cardiolipin autoantibody level [24]. However, rare study of cystamine in liver apoptosis in SLE is investigated. In this study, we identified the protective effects of cystamine in liver from NZB/W F1 mice against apoptosis.

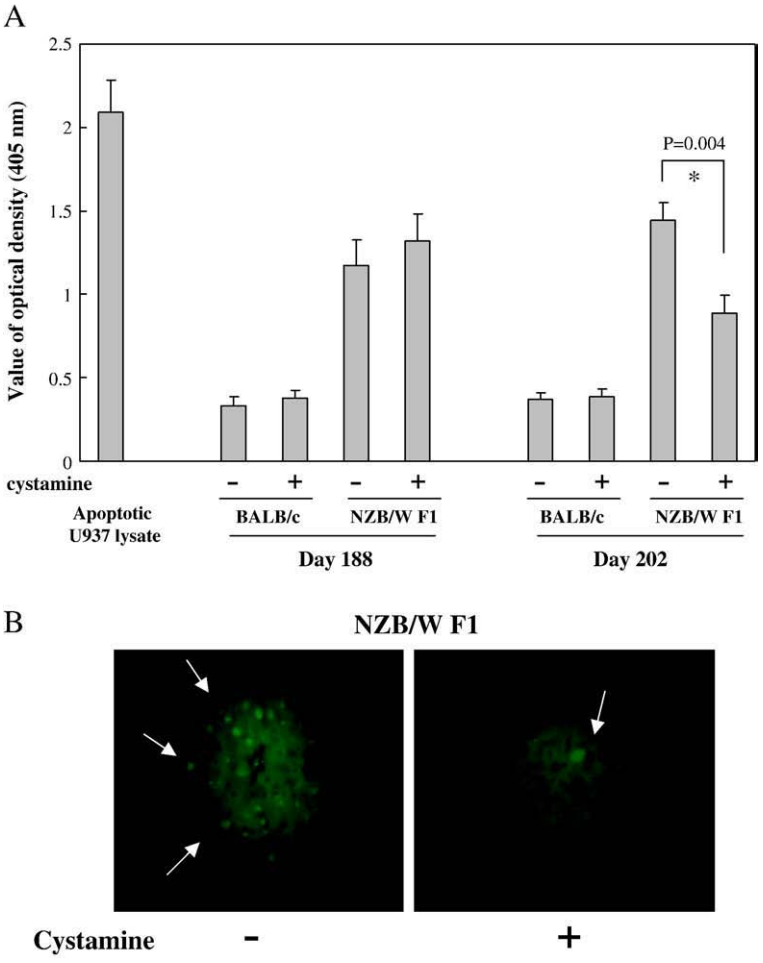

Figure 1 Detection of apoptosis. (A) Activity of caspase-3 was measured in 20 μg liver lysates from BALB/c or NZB/W F1 mice that were given PBS or cystamine at the age of 188-day or 202-day, respectively. The UV-induced apoptotic U937 lysate comes along with the kit was used as positive control. (B) TUNEL assay of liver sections from NZB/W F1 mice given PBS or cystamine. FITC-labeled terminal deoxy-transferase was bound to nicked end of DNA as arrows indicated. Three independent experiments were performed and * indicates significant difference.