HO-1 蛋白在砷化物誘導的角質細胞增生角色之研究

The study of Heme Oxygenase-1 in the proliferation of keratinocytes by arsenic compounds

中文摘要

砷是公認的人體致癌物之一。最近地下水含砷影響人類健康引起社會上史無前例的關心，而且到目前爲止經由何種機轉形成癌症仍然不是非常清楚。在砷化物的代謝過程中，無機砷會被代謝成具有甲基的代謝產物，包含單甲基(Monomethylarsonic acid/MMA) 及雙甲基(Dimethylarsinic acid/DMA) 化合物，最後經由尿液排出體外。熱休克蛋白 (Heat shock proteins) 是細胞承受壓力時出現的保護性蛋白。其中，Heme oxygenase-1(HO-1) 蛋白的表現似乎與砷的暴露有高度的關聯性。在其他文獻及本篇中探討由砷化物所誘發的過氧化物會影響皮膚細胞中的相關蛋白質，進而加速細胞增生的速度。本研究主要是探討砷化物及其代謝產物 (As+3, As+5, MMA+3, DMA+3, MMA+5and DMA+5) 誘導的皮膚細胞增生過程中，HO-1 所扮演的角色。研究結果顯示，低劑量(1 M 和 0.5 M) 的 As+3 和 MMA+3 會促進皮膚角質細胞 (HaCaT) 的細胞增生作用，而 HO-1 蛋白的表現量也隨著砷化物的處理有增加的趨勢。其中，砷化物可能透過的機轉包括 ERKs、 JNKs 和 p38 三條路徑，彼此間確實有明顯的不同。利用 HO-1 蛋白的抑制劑 (SnPP)，確實可以部分抑制細胞的增生作用。因此證實 HO-1 蛋白在砷化物誘導的皮膚細胞增生過程中，參與部分重要的角色。

英文摘要

Arsenics have been considered the most potential human carcinogen. Recently the issue of arsenic in drinking water raised an unprecedented social concern on human health, and yet the molecular mechanisms through which arsenic induces cancer remain unknown. In the process of arsenic metabolism, inorganic arsenic is methylated to monomethylarsonic acid (MMA) and finally to dimethylarsinic acid (DMA), followed by excretion through urine. Heat shock proteins, which protect cells from stress will be induced when cells suffer from different kind of stimulates. Evidence support that HO-1 protein is highly correlated to the exposure of arsenic. We and others hypothesis which arsenic-induced formation of reactive oxygen species and the subsequent activation other protein in the skin, leading to increase in cell proliferation. The specific aim of this study is to investigate the role of HO-1 on the proliferative mechanism of arsenics and their metabolites, including As+3, As+5, MMA+3, DMA+3, MMA+5 and DMA+5 treated HaCaT cells. Among the arsenics and its metabolites, low doses (1 M and 0.5 M) As+3 and MMA+3 show the

potent proliferative effect in HaCaT cells, and HO-1 protein induction was correlated to arsenic exposure. Besides, the signal transduction pathway, including ERKs、JNKs and p38 involved in arsenic and its metabolites are totally different. The HO-1 inhibitor (SnPP) attenuated arsenic induced HaCaT cells proliferation. Results of our study provide evidence to suggest HO-1 may in arsenics induced proliferation involve in arsenics.