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Sulforaphane mitigates genotoxicity induced by radiation and anticancer drugs in human lymphocytes

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ABSTRACT

Sulforaphane, present in cruciferous vegetables such as broccoli, is a dietary anticancer agent. Sulforaphane, added 2 or 20 h following phytohemaglutinin stimulation to cultured peripheral blood lymphocytes of individuals accidentally exposed to mixed γ and β-radiation, reduced the micronucleus frequency by up to 70%. Studies with whole blood cultures obtained from healthy volunteers confirmed the ability of sulforaphane to ameliorate γ-radiation-induced genotoxicity and to reduce micronucleus induction by other DNA-damaging anticancer agents, such as bleomycin and doxorubicin. This reduction in genotoxicity in lymphocytes treated at the G_0 or G_1 stage suggests a role for sulforaphane in modulating DNA repair. Sulforaphane also countered the radiation-induced increase in lymphocyte HDAC activity, to control levels, when cells were treated 2 h after exposure, and enhanced histone H4 acetylation status. Sulforaphane post-irradiation treatment enhanced the CD 34$^+$Lin$^-$ cell population in culture. Sulforaphane has therapeutic potential for management of the late effects of radiation.

1. Introduction

Development of radioprotective agents is of interest for applications in defence, the nuclear power industry, radiation accident response, space flight, and reducing damage to normal tissues during cancer radiotherapy. Progress has been made in development of prophylactic agents that reduce biological damage when administered prior to exposure, although amifostine (an amino thiol; WR-2712, originally developed at Walter Reed Army Institute, USA) remains the only radioprotective agent approved by the US FDA [1]. Therapeutic management of radiation-exposed persons makes use of standard supportive care drugs and growth factors, generally administered following the appearance of symptoms. The development of approaches for mitigation [2] of radiation damage has received attention only recently. An ideal radiomitigating agent would provide benefit against both acute and delayed effects of ionizing radiation when administered orally, soon after exposure.

Acute and late effects of ionizing radiation arise due to macromolecular damage, especially DNA double strand breaks. Cellular repair and recovery involve multiple damage response pathways regulating DNA repair, cell cycle perturbations, cell death, etc., activated soon after damage induction, and determining subsequent survival, transformation, and mutation. The accessibility of DNA in chromatin, an important determinant of response, is regulated by post-translational modifications (especially acetylation) of histones, among other factors. Acetylation and deacetylation of histone and non-histone proteins are tightly regulated by the opposing effects of HATs (Histone Acetyltransferase) and HDACs (Histone Deacetylase), respectively [3,4]. Modifiers of HATs and HDACs affect cellular responses to radiation [4]. HDAC inhibitors have shown radioprotective activity in animal models, especially against late effects of radiation [3,5]. Sulforaphane (SFN) is an HDAC inhibitor present in broccoli [4]. SFN also affects the Nrf-2-Keap system [6,7]. Here, we report the ability of SFN to mitigate radiation-induced genotoxicity under *in vitro* conditions, in cultured peripheral blood samples from a cohort of accidentally radiation-exposed individuals.

The blood samples used in this study were obtained from persons referred to INMAS for the assessment of radiation doses received by individuals who were exposed due to the negligent dismantling of a Co-60 gamma source in Delhi [8,9]. The gamma irradiator was imported to India in 1968, with an estimated initial strength of approximately 3600 Ci, and was disposed in March 2010. The scrap dealer tried to dismantle the instrument, leading to the exposure of workers and other persons. Some individuals spent 12–14 h per day near the source, which led to a relatively higher exposure and subsequent radiation sickness symptoms, prompting hospitalization of 5–7 persons. The highest estimated

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