SIGNALING PATHWAYS AND INTRACELLULAR TARGETS OF SULFORAPHANE-MEDIATED ANTILEUKEMIC POTENTIAL

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The association of decreased cancer risk with intake of cruciferous vegetables is stronger than that reported for fruit and vegetables in general. An active constituent in cruciferae is sulforaphane (SF). In vitro and in vivo studies have reported that SF affects many steps of cancer development. It can modulate early stages of carcinogenetic process or affect events, such as apoptosis, cell proliferation and angiogenesis more specifically involved in the promotion and progression phases. Activation of apoptosis and cell-cycle regulation pathways is a convergence point for many cytotoxic agents, independent of specific drug mechanisms. SF is a potent proapoptotic agents in a wide variety of cancer cells both in vitro and in vivo, including acute lymphoblastic leukaemia cell lines. Acute lymphoblastic leukaemia is a malignant disease of the bone marrow in which early lymphoid precursors proliferate and replace the normal hematopoietic cells of the marrow. A poor prognosis of acute lymphoblastic leukaemia patients is related to the recurrence in the bone marrow, a hypoxic tissue compartment. It has been documented that the hypoxic tissue may serve as a "sanctuary" site for tumour cells, resulting in resistance to many common chemotherapeutic agents due to hypoxia. Therefore, we were interested in identifying whether hypoxia could exert an inhibitive effect on the sensitivity of acute lymphoblastic leukemia cells to SF. In particular, we investigated the cytotoxic and proapoptotic potential of SF and its ability to modulate cell-cycle progression of human T lymphoblastoid cells in hypoxic conditions (1.5% O_2). The results were then compared with those obtained in normoxia (20% O_2). SF-induced apoptosis and cytotoxicity was reduced by hypoxia. However, the effect was both quantitatively and qualitatively different. For example, higher concentrations but shorter exposures to SF were necessary for inducing apoptosis in hypoxia than in normoxia. An increase in the percentage of G1 cells was recorded in hypoxic conditions, whereas an increase in the G2/M cells was observed in normoxic conditions. Considering these pronounced differences, we performed the gene expression profile in leukaemia cells treated with SF both in normoxia and hypoxia using Agilent microarray. SF regulated different set of genes of known importance in suppression of the cell cycle and induction of apoptosis. However, some molecular pathways modulated by SF are specifically involved only in hypoxic conditions. These aspects can allow to fully understand the exact mechanism of action of SF and indicate an important new avenue for future researches on clinical applicability of SF to cancer patients.