Promising Selectivity of Dietary Isothiocyanates from Cruciferous Vegetables for Human Cancer Cells

A. Melchini,[a,b] P. Maimone,[c] M. Francisco,[d] M. Traka,[b] R. Mithen,[b] A. Trovato,[c] R. De Pasquale[c]

[a]Fondazione "Prof. Antonio Imbesi", Università di Messina, P. zza Pugliatti 1, Messina, Italia; [b]Plant Natural Products and Health Programme, Institute of Food Research, Norwich Research Park, Norwich, United Kingdom; [c]Dipartimento Farmaco-Biologico, Facoltà di Farmacia, Università di Messina, Vill. Annunziata, Messina, Italia; [d] Misión Biológica de Galicia (CSIC), PO Box 28, Pontevedra, Spain.

Consumption of cruciferous vegetables has been associated with a reduced risk in development of various types of cancer [1]. This has been attributed to the bioactive hydrolysis products that are derived from these vegetables, namely isothiocyanates (ITCs) [2]. A growing body of evidences from cell and animal models indicates several molecular mechanism of chemoprevention by ITCs, that include modulation of phase I, II and III detoxification, regulation of cell growth by induction of apoptosis and cell cycle arrest, induction of ROS-mechanisms and regulation androgen receptor pathways [3]. Literature data present current knowledge on these mechanisms of action of ITCs in cancer cell lines to date. However, a primary goal in the anticancer drugs research is the discovery and development of functional molecules characterized by selective cytotoxicity against cancer cells and low toxicity for healthy cells. At present, the effect of ITCs in normal cells has not been fully investigated. There is evidence that the 4-(methylthio) butyl isothiocyanate (erucin, ER) is able to induce a strong antiproliferative effect on human leukemia cells, but not in non-transformed human peripheral T lymphocytes [4]. Recently, the selectivity of β-phenylethyl isothiocyanate (PEITC) against oncogenically transformed ovarian epithelial cells, including cisplatin-resistant cells, has been reported [5]. The aim of this study was to evaluate the differential response of both normal and cancer cells from human prostate to ER and its oxidized analog, the 4-(methylsulfinyl) butyl isothiocyanate (sulforaphane, SF). The effect of increasing concentrations of SF and ER on two different human prostatic cell lines, normal prostate epithelium (PNT1A) and prostate adenocarcinoma cells (PC3) was determinate, and we went on to provide additional mechanistic information in relation to the potential selectivity for cancer cells. Our preliminary data demonstrate that these structurally related ITCs exert a specific action on oncogenic signalling pathways, such as p53/p21 and extracellular signal-regulated kinases (ERK) 1/2 pathways, that could explain the stronger cytotoxicity observed in cancer cells compared to non malignant cells. Although these dietary bioactive compounds have exhibited selectivity for oncogenically transformed cell lines, ITC selectivity is an area of great interest that warrants further investigation.

Riferimenti [1] J. V. Higdon, B. Delage, D.E. Williams, R.H. Dashwood *Pharmacol Res* **2007,** *55*, 224-236; [2] J. D. Hayes, M.O. Kelleher, I. M. Eggleston *Eur J Nutr* **2008,** *47*, 73-88; [3] Y. Nakamura *Forum Nutr* **2009,** *61*, 170-181; [4] C. Fimognari, M. Nusse, R. Iori, G. Cantelli-Forti, P. Hrelia *Invest New Drugs* **2004,** *22*, 119-129; [5] D. Trachootham, Y. Zhou, H. Zhang, Y. Demizu, Z. Chen, H. Pelicano, P.J. Chiao, G. Achanta, R.B. Arlinghaus, J. Liu, P. Huang *Cancer Cell* **2006,** *10*, 241-252.