The chemopreventive effects of isothiocyanate moringin isolated from Moringa oleifera seeds

1)Vivarelli F. 2)Paolini M. 3)Michl C. 4)Rascle A. 5)Weigl J. 6)De nicola G. 7)Iori R. 8)Cirillo S. 9)Canistro D.

University of Bologna

Over the past years, there has been a growing interest in the natural constituents of vegetables as a potential means of cancer control. Isothiocyanates (ITCs) are considered as ideal chemopreventive agents, due to their abundance in easily accessible brassica vegetables, their ability to target multiple pathways involved in cancer aetiology coupled with a favourable toxicological profile. Recently it was reported that sulphoraphane (SFN) inhibits STAT5-mediated transcription. STAT5 (Signal Transducer and Activator of transcription 5) belongs to a family of transcription factors (STAT1-6) mainly present in an inactive form in the cytoplasm of numerous cell types and which are activated by phosphorylation in response to specific cytokines hormones and growth factors. STAT5 plays a key role in the control of cell proliferation and survival, via the regulation of genes such as c-Myc, Pim-1, Bcl-x, Osm or Cis and it also contributes to immune cell differentiation and function. Its activity is normally tightly controlled, and is hence frequently found deregulated in cancer where it is often constitutively activated. For these reasons STAT inhibitors are considered as potential candidates for cancer prevention or therapy. Beside SFN, more recently the isothiocyanate moringin (GMG-ITC), isolated from the Moringa oleifera, has caught the interest of scientific community for its anti-inflammatory activity through the inhibition of the NF-κ B pathway and it showed interesting anti cancer effects against mouse multiple myeloma and human astrocytoma cell line. However, till now, very little is known about the activity of GMG-ITC on cell signaling pathways.

The present study was conceived to explore the potential inhibitory effect of GMG-ITC on crucial pathways commonly up-regulated in cancer, such as JAK/STAT and NF-κB comparing results with those obtained with SFN. Results showed how SFN and GMG-ITC were able to suppress IL-3-induced expression of STAT5 target genes in mouse pro-B cells, however, GMG-ITC reported a stronger inhibitory activity compared to SFN. Both GMG-ITC and SFN did not inhibit STAT5 phosphorylation, suggesting a downstream inhibitory event. Expression of interferon (IFNα)-stimulated STAT1/STAT2 target genes (G1P3, ISG15, STAT1, IRF9) in HeLa cells were down-regulated by GMG-ITC and SFN without altering STAT1 and STAT2 phosphorylation. Also in this case GMG-ITC exhibited a more marked activity then those observed with SFN. Notable, basal expression of c-Myc remained unaffected upon treatment with up to 10 μM SFN or GMG-ITC, indicating that both ITCs inhibit STAT5-induced but not basal c-Myc. GMG-ITC and SFN had a limited effect on IFNα-induced STAT1 and STAT2 activity, indicating that both ITCs differentially target JAK/STAT signaling pathways. Furthermore, we showed that GMG-ITC in the micromolar range is a more potent inhibitor of TNF-induced NF-κB activity than SFN. TNF-induced expression of IL-8 and IL-6 was inhibited by both SFN and GMG-ITC, but this last appeared to be more effective. Interestingly, SFN and GMG-ITC inhibit NF-κ B signaling with a greater potency than that mediated by the well-known NF-κB inhibitor curcumin. As a whole, our data indicate how GMG-ITC could be considered as a potent inhibitor of STAT5, NF-κ B as well as STAT1/STAT2 signaling pathways, often overcoming the effects obtained with SFN. Given the implication of these

pathways in the carcinogenesis, inflammatory diseases and immune disorders, GMG-ITC could represent a newsworthy and attractive chemopreventive agent.