S-IV-4

NOVEL LEAD STRUCTURES AND MECHANISMS FOR CANCER CHEMOPREVENTION

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Nutrition influences cancer incidence and offers a variety of preventive dietary factors including non-nutritive plant metabolites. To identify novel potential chemopreventive agents, we have set up cell- and enzyme-based *in vitro* marker systems relevant for prevention of carcinogenesis *in vivo*. This experimental approach led to the identification of Xanthohumol (Xn), a prenylated chalcone from hop (*Humulus lupulus* L.) as a most promising broad-spectrum chemopreventive agent. Xn was able to modulate drug metabolism and to scavenge reactive oxygen species. It was identified as an anti-inflammatory agent by inhibition of cyclooxygenase (Cox) 1 and 2 activity. Xn further prevented lipopolysaccharide-mediated induction of inducible nitric oxide synthase (iNOS). Anti-proliferative mechanisms included anti-estrogenic properties, inhibition of DNA polymerase α and induction of apoptosis and cell differentiation. Most importantly, Xn at nanomolar concentrations prevented carcinogen-induced preneoplastic lesions in mouse mammary gland organ culture (MMOC), providing a first direct proof for its chemopreventive potential (1). Investigations on bio-availability, efficacy and safety in animal models are ongoing.

Liverworts (*Hepaticae*), a category of mosses, are a unique source of bibenzyl derivatives of lunularic acid. These compounds display structural similarities with resveratrol found in grapes and red wine and were identified as potent modulators of phase 1 and phase 2 metabolizing enzymes. Induction was dependent on a xenobiotic-response element (XRE)-mediated bifunctional mechanism, although the compounds have no similarity to known ligands of the aryl hydrocarbon (Ah) receptor. Selected compounds were identified as competitive inhibitors of Phase 1 Cyp1A activity. Ei252, a synthetic

derivative with a bromo-substituted thiophene ring system, inhibited preneoplastic lesions in the MMOC model with an IC_{50} value of 190 nM, and was identified as an extremely potent inhibitor of benzo(*a*)pyrene-mediated transformation of primary rat tracheal epithelial cells, with an IC_{50} value < 10 nM. Based on these results, bibenzyls will be further investigated as readily available promising new cancer chemopreventive agents.

Beside facilitating the identification of novel lead structures, *in vitro* systems are useful for the elucidation of chemopreventive mechanisms. Aiming to investigate the anti-inflammatory potential of sulforaphane (SFN), we detected a potent decrease in LPS-induced secretion of pro-inflammatory and pro-carcinogenic signaling factors in cultured Raw 264.7 macrophages after SFN-treatment, i.e. nitric oxide (NO), prostaglandin E_2 (PGE_2) and tumor necrosis factor (TNF-α). LPS-induced iNOS protein expression was suppressed at the transcriptional level, and nuclear factor B (NF-κB) was identified as a the key mediator. SFN selectively reduced DNA-binding of NF-B without interfering with LPS-induced degradation of I-κB (inhibitor of NF-κB) nor with nuclear translocation of NF-κB. Rather, we demonstrated that time-dependent modulation of GSH levels by SFN might influence NF-κB DNA-binding (2). As an additional redox-regulatory mechanism, we have identified SFN as a novel inhibitor of thioredoxin reductase. Taken together, our data provide evidence that anti-inflammatory mechanisms contribute to SFN-mediated cancer chemoprevention (funded by Verein zur Förderung der Krebsforschung in Deutschland und Wissenschaftsförderung des Deutschen Brauerbunds e.V.).

References:

(1) Gerhauser, C. *et al.* Hop(e) for cancer prevention - Chemopreventive activity of Xanthohumol, a prenylated chalcone from hop (*Humulus lupulus* L.) (submitted).

(2) Heiss, E. *et al.*, Nuclear factor-κB is a molecular target for sulforaphane-mediated anti-inflammatory mechanisms. *J. Biol. Chem.* (in press).