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Nutri-epigenetics and cancer chemoprevention

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Within the past decade, epigenetic mechanisms and their modulation by natural products have gained major interest in the chemopreventive community. The term “epigenetics” refers to modifications in gene expression caused by heritable, but potentially reversible, changes in DNA methylation and chromatin structure. Major epigenetic mechanisms include DNA hyper- and hypomethylation, histone acetylation and methylation (among others), and non-coding (micro) RNAs. Given the fact that epigenetic modifications occur early in carcinogenesis and represent potentially initiating events in cancer development, they have been identified as promising new targets for prevention strategies.

Chemopreventive agents from various dietary sources, including green tea, soy, fruit and berries, cruciferous vegetables, turmeric and others were shown to directly target enzymatic activities or modulate expression of enzymes involved in epigenetic gene regulation, including DNA methyltransferases, histone acetyltransferases, deacetylases and demethylases, as well as sirtuins. Also, many cancer preventive compounds were shown to alter miRNA expression. Research over the last decade is accumulating that these activities might contribute to their chemopreventive efficacy by effects on signal transduction mediated by nuclear receptors and transcription factors such as NF-κB, cell proliferation and cell cycle progression, cellular differentiation, DNA repair, apoptosis induction, cell motility, metastasis formation, and cellular senescence. So far, evidence of *in vivo* epigenetic activities in animal models and human pilot studies are limited (see recent reviews for additional information).

- As an example, **(-)-epigallocatechin gallate (EGCG)** from green tea was the first chemopreventive agent reported to inhibit DNA methyltransferase activity *in vitro*, and to reduce promoter hypermethylation of selected candidate genes in cell culture and in selected animal models. Results were however not always reproducible. EGCG treatment also decreases histone methylation and induces miRNA expression, thereby reducing cancer cell survival by modulating the expression of cell cycle and apoptosis-regulating proteins. Interestingly, recent reports indicate that combinations of bioactives targeting different epigenetic mechanisms might be more effective than each single compound alone, for example by combining green tea extracts with HDAC inhibitors.
- Gary Stoner and colleagues investigated in colon cancer patients potential epigenetic effects of a dietary intervention with freeze-dried **black raspberries** rich in ellagic acid and anthocyanidins. They discovered re-expression of silenced genes of the Wnt signalling pathway through reduction of promoter methylation (Wang et al., 2011). These data were recapitulated in rodent models for ulcerative colitis. Comparative *in vitro* analyses revealed that anthocyanidins might be the active components through downregulation of DNA methyltransferases.
- Inhibition of histone deacetylase activity by a metabolite of **sulforaphane from broccoli** results in histone hyperacetylation, opening of the chromatin, and increased expression of genes regulating cell cycle progression and apoptosis, both *in vitro* and in animal and human pilot studies.
- The **soy isoflavone genistein** affects DNA methylation, histone modifying enzymes and miRNA expression, thereby modulating hormone receptor signaling and cell growth. Our recent research indicates that the timing of isoflavone exposure might influence its effects on DNA methylation, at least in rats (Pudenz et al., in preparation).
- Anti-inflammatory and apoptosis-inducing activities of **curcumin, a component of curry**, are mediated by various epigenetic mechanisms, targeting the transcription factors NF-κB and p53. Curcumin was also shown to modulate the expression of both oncogenic and tumor suppressive miRNAs with major functions in regulating cell proliferation, motility and stem-cell like properties.

Outlook: Current epigenetic research is highly dynamic field. With the available technologies for quantitative methylome profiling (e.g. Illumina 450k bead arrays for human samples, reduced

representation and whole genome bisulfite sequencing (RRBS, WGBS)), future studies will have to focus on genome-wide analyses, integration of effects on various epigenomic mechanisms with gene expression, and the link to chemopreventive outcome, to identify best strategies for chemopreventive intervention targeting the epigenome.

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Recent reviews for further reading (available from our website):

Huang J, Plass C, Gerhauser C. Cancer Chemoprevention by Targeting the Epigenome. Curr Drug Targets 2011; 12: 1925-56.

Gerhauser C. Cancer chemoprevention and nutriepigenetics: state of the art and future challenges. Top Curr Chem. 2013; 329: 73-132.

Gerhauser C. Epigenetics, Plant (Poly)phenolics and Cancer Prevention. Chapter 6 in: Recent Advences in Polyphenol Reseach Vol.4 (Editor Stephane Quideau), Wiley-Blackwell 2014

Pudenz, M., Roth, K., Gerhauser, C. Impact of Soy Isoflavones on the Epigenome in Cancer Prevention (Review). Nutrients (Special issue Nutritional Epigenetics) 2014; 6: 4218-72.

Gerhauser, C., Heilmann, K., Pudenz, M. Genome-wide DNA methylation profiling in dietary intervention studies – A users' perspective. Curr. Pharmacol. Rep. 2015; doi:10.1007/s40495-014-0001-y

Wang, L.S. et al., Modulation of genetic and epigenetic biomarkers of colorectal cancer in humans by black raspberries: a phase I pilot study. Clin. Cancer Res. 2011; 17: 598-610.