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The Principle Tenet in Oncology

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"The principle tenet in oncology – that cancer is a disease initiated and driven by genetic anomalies – remains uncontested, but it is now clear that epigenetic pathways also play a significant role in oncogenesis."[i] Many phytochemicals have been studied for their preventive and epigenetic effects. "Numerous investigations have described epigenetic alterations modified by dietary factors, focusing on their ability to act as histone modifiers and DNA methyltransferases inhibitors."[ii] "DNA methylation, histone modification, and alterations to microRNA (miRNA) expression are the most common methods of epigenetic modifications."[iii] (Because histone acetylation and DNA methylation are driven by constant cell signals, the physical structure of the genome is dynamic. [i.e. gene on or gene off]). In other words, phytochemicals can act on the DNA's epigenetic 'tags' that influence genetic expression.

"Epigenetics encompasses a collection of mechanisms that define the phenotype of a cell without affecting the genotype. In molecular terms, it represents a range of mechanism, including DNA methylation, histone modification, remodeling of nucleosomes and higher order chromatin reorganization, and regulation by noncoding RNAs. A key characteristic of the epigenetic signal is that it is heritable and can be passed from somatic cell to daughter cell during mitosis and even across the generations during meiosis."[vi]

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Historically, cancer is the disease in which epigenetics has been studied most extensively. A common observation in human tumors is epigenetic change, including altered methylation of DNA and the histones associated with DNA. Hypomethylation in tumor cells is thought to be an early trigger that predisposes cells to genome instability and hypermethylation of specific genes thought to be involved in carcinogenesis and disease progression."[v] "Certain imprinted genes (see explanation of imprinted genes below) are known tumor suppressors involved in cell proliferation. Loss of imprinting (gain or loss of DNA methylation or loss of allele-specific gene expression) is also a common characteristic of many cancer types, including breast, lung, colon, liver, and ovary." [vi]

["For most genes, we inherit two working copies - one from mom and one from dad. But with imprinted genes, we inherit only one working copy. Depending on the gene, either the copy from mom or the copy from dad is epigenetically silenced. Silencing usually happens through the addition of methyl groups during egg or sperm formation. The epigenetic tags on imprinted genes usually stay put for the life of the organism. Imprinted genes are especially sensitive to environmental signals. Because imprinted genes are only a single active copy and no back up, any epigenetic changes or "epimutations" will have greater impact on gene expression. Environmental signals can also affect the imprinting process itself. Imprinting happened during egg and sperm formation, when epigenetic tags are added to the silence specific genes. Diet, hormones and toxins can all affect this process, impacting the expression of genes in the next generation."[vii] For example, exposure to certain dioxin compounds induces DNA methylation in imprinted genes]. [viii]

[Simplified version of epigenetic: DNA contains the instructions for building all the parts of the body. The DNA is wrapped around proteins called histones. Both the DNA and histones are covered with chemical tags. This second layer of structure is called the epigenome. The epigenome shapes the physical structure of the genome. It tightly wraps inactive genes making them unreadable. It relaxes active genes making them easily accessible. Different sets of genes are active in different cell types. The DNA code remains fixed for life, but the epigenome is flexible. Epigenetic tags react to signals from the outside world such as diet and stress. The epigenome adjust specific genes in our genomic landscape in response to our rapidly changing environment.]

The epigenetic modulation of cancer by dietary phytochemicals has been studied due to their potential role in cancer prevention. "The chemoprotective effects of several dietary phytochemicals are thought to protect against the development of tumors and inhibit or prevent cancer initiation and progression. Dietary polyphenols are also attractive therapeutic agents because of their low rate of toxicity and their ability to reverse epigenetic modifications affecting aberrantly expressed genes (see table below). Also, in vivo and in vitro investigations have demonstrated that several dietary components can inhibit cancer cell proliferation."[ix]

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Categories of Dietary Phytochemicals [x]

CATEGORIES OF PHYTOCHEMICALS	PRIMARY DIETARY SOURCES	CHEMOPROTECTIVE EPIGENETIC PROPERTIES
Polyphenols	Green tea, turmeric, curry, soybeans, kudzu, fava beans, grapes, red wine, peanuts, mulberry, cranberry, blueberry.	DNA methyltransferases inhibitor Histone acetyltransferases inhibitor Histone deacetyltransferases inhibitor Modify miRNA (microRNA)
Organosulfur compounds	Broccoli, cabbage, kale, mushrooms, onions, watercress, garlic, Brazilian nuts, chicken, game meat, beef.	DNA methyltransferases inhibitor Histone deacetyltransferases inhibitor
Carotenoids	Carrots, squash, tomatoes, corn, spinach.	Indices DNA methylation and demethylation - Modify histones
Alkaloids	Coffee, nicotine.	Inhibit DNA methylation

(MicroRNA = Short non-coding RNAs expressed in different tissue and cell types that suppress the expression of target genes. As such, microRNAs are critical cogs in numerous biological processes and dysregulated microRNA expression is correlated with many human diseases)" [xi]

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End Notes

[i] *Dawson MA, Kouzarides T. cancer Epigenetics: From Mechanism to Therapy. Cell 150. 6 July 2012: 12 - 27.*
[ii] *Hardy TM, Tollefsbol TO. Epigenetic Modifications by Dietary Phytochemicals in Cancer Prevention. In: Kong AT. Inflammation, Oxidative Stress, and Cancer; Dietary Approaches for Cancer Prevention. Boca Raton: CRC Press; 2014. p. 578.*
[iii] *Ibid. 577.*
[iv] *Haggarty P. Epigenetics. In: Ross AC, Caballero B, Cousins RJ, Tucker KL, Ziegler TR. Modern Nutrition in Health and disease. 11th Ed. Baltimore: Lippincott Williams & Wilkins; 2014. 534.*
[v] *Ibid.*
[vi] *Ibid.*
[vii] *www.learn.gentics.utah.edu/content/epigentics/control*
[viii] *Kanherkar RR, Bhatia-Dey N, Csoka AB. Epigenetics across the human lifespan. Front Cell Dev Biol. 2014; 2:29.*
[ix] *Hardy TM, Tollefsbol TO. Epigenetic Modifications by Dietary Phytochemicals in Cancer Prevention. In: Kong AT. Inflammation, Oxidative Stress, and Cancer; Dietary Approaches for Cancer Prevention. Boca Raton: CRC Press; 2014. p. 578.*
[x] *Ibid. 579.*
[xi] *Cheng CJ, Bahal R, Babar IA, Pincus Z, Barreera F, Liu C, et al. MicroRNA silencing for cancer therapy targeted to tumor microenvironment. Nature. 05 Feb 2015; 518: 107-110.*

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