



CANCER AND EPIGENETICS INTERRELATIONSHIP IN PREVENTION AND CURE

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ABSTRACT

Epigenetics (Lifestyle) is a new field of biology that is exploring the effect of the environment on cellular behavior. The "environment" includes one's physical, social, and electromagnetic environment as well as beliefs, perceptions, lifestyle, habits, behaviors, and mind-body practices such as Pranic healing. With the science of epigenetics, we can begin to map out genes that keep us in a healthy state and eliminate those bad genes that have been plaguing humans over the course of time. There is real possibility to prevent and cure for certain cancers & other dreadful diseases.

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INTRODUCTION

Epigenetics is the study of how we can change the expression of our genes without changing the sequence of the actual DNA or the genetic code. "Epi" comes from the Greek word meaning *over, above, or outer*. Epigenetics is the study of changing genetics without actually touching the genes. Epigenetics (Lifestyle) (literally, control beyond genetics) is a new field of biology that is exploring the Effect of the environment on cellular behavior. The "environment" includes one's physical, social, and electromagnetic environment as well as beliefs, perceptions, lifestyle, habits, behaviors, and mind-body practices such as Pranic healing. There are two primary and interconnected epigenetic mechanisms - DNA methylation and covalent modification of histones. In addition, it is also becoming apparent that RNA is intimately involved in the formation of a repressive chromatin state. An epigenetic factor is something that affects genes without changing the nucleotide sequence and which can be inherited through cell division.

Epigenetic mechanisms (or "marks") involve the addition or removal of small chemical groups (e.g. commonly methyl or acetyl groups) to or from DNA bases or chromatin. Epigenetics is the key to reading the genetic code in different ways and ultimately altering the code to coax disease cells, which begin as normal cells, to return to their proper behavior. This area of research holds such great promise that the National Institutes of Health has designated it as a major "Roadmap" initiative to speed its development. The study of epigenetics has the potential to explain the mechanisms that lead not only to cancer, but to aging, heart disease, mental health and other conditions.

Epigenetics and Ayurveda

There is an old saying in Ayurveda that goes, "what you see, you become." It's an ancient take on epigenetics. If your environment can change your genetic expression, then it seems wise to surround yourself with a healthy environment rich in peace, love and joy rather than stress, violence and exhaustion. *Ayurveda* is the study of life science. *Ayu* – meaning life and *Veda* – meaning science or knowledge. This science has been witnessed and practiced for 5000 years since the ancient Vedas

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were written. Ayurveda believes that the origin of disease is rooted in one key phrase, "Forgetting our true nature as spirit." This can be further explained by understanding a little bit of Samkhya philosophy. Purusha desires to know its own nature and merges with Prakriti. What unfolds is the creation of the individual soul. It is believed that disease unfolds when a person forgets their true nature as spirit. This happens at every incarnation. At each incarnation there is a storehouse of karma that is stored in the causal body. When incarnation occurs the ahankara takes form into an astral body where disturbance originates. These disturbances of the mind called vrittis upset the balance of a person which then manifests into the physical body as disease states. In one of the most classically cited books on Ayurveda, the *Charaka Samhita* states, "The soul is essentially devoid of all pathogenicity..." once we forget our true nature as spirit we then can start manifesting disease in the astral body. These disturbances that begin in the mind then start affect the physical body creating imbalance to the *Doshas*. This is not only genetically determined (*ShukraShonita*), but also influenced by environment (*MahabhutaVikara*), chiefly by maternal diet and lifestyle (*Matura Ahara Vihara*), and the age of the parents (Kala Ethnicity (*Jati*), familial characteristics (*Satmya*), as well as place of origin of an individual (Desha) are also considered to influence the development of *Prakriti*..." *Prakriti* is determined by our parents' nature, as well as the circumstances of our birth. (*Garbhashaya*). Our mother's emotional and physical state, the season, and location of our birthplace are all determining factors in our *Prakriti*. According to Ayurveda this happen at the moment of conception and the lifestyle of our mother will play a role in the development of the offspring but the seeds of karma are also a factor in determining the tendency of the offspring.

Prakruti vs. Vikruti

We are born into this world with a predetermined set of tendencies. Our *Prakruti* in Ayurveda roughly resembles our DNA, or our genes, in western medicine. Each of us is born with a unique constitutional balance. This is known as our *Prakruti*. In Ayurveda the individual constitution, or *Prakruti*, is based on physical and psychological characteristics. "Prakriti is a corollary of the comparative proportion of three entities, i.e., *Tridoshas*, namely, *Vata*, *Pitta*, and *Kapha*. So, if our *Prakruti* is roughly related to our genes then our *Vikruti* is roughly related to our phenotype in Epigenetics. Our *Vikruti* is defined as the nature of the imbalance. It is our current state. *Prakruti* is determined at the moment of conception and our *Vikruti* is the present state of the person. To get from point A (*Prakruti*) to point B (*Vikruti*) there can be any number of changes and those changes relate to epigenetic factors that include sensory input from the outside world. This includes diet, lifestyle, visual input, sensory stimulation, emotions, as well as many other environmental factors. Personalized Preventative Medicine (PPM) has been at the forefront of study in recent times. Modern science is realizing that epigenetic factors (i.e. diet, lifestyle, season, time of life, and individual tendencies) are directly influencing drug response. By taking the knowledge of modern science and combining it with the roots of Ayurveda, there is an opportunity to change the course of some of the most plaguing disorders of the modern world today. This includes diet, lifestyle, visual input, sensory stimulation, emotions, as well as many other environmental factors. According to Ayurveda, any state that is not at *Prakruti* is a state of dis-ease and in

order to treat this one must know the nature of the patient, the nature of the disease and the nature of the remedy. Dis means having a negative or reversing force. Ease means free from difficulty, effort, or trouble. Dis-ease, therefore, is a negative reversal of the flow of ease. Ayurveda's holistic approach to treating the mind, body and soul as a complete person has the potential to solve some of the world's most pressing health problems. Modern medicine has seen this need for personalized medicine and Ayurveda offers the path which plays a key role towards disease prevention through diet and lifestyle. According to *Ayurveda* treatment of the disease does not treat the symptoms but brings the person back to their true nature. The body will then be able to rid itself of the disease. The *Charaka Samhita* states, "So the unwholesome conjunction of the sense organs with their objects, intellectual blasphemy (*Pragyaparadha*) and transformation (*Parinama*) – these are the threefold cause of diseases. Proper utilization of the objects, action and time is beneficial to the maintenance of normal health." Dr. Grasser is one of the world's foremost experts in the integration of Functional Medicine and *Ayurveda*. "If you have a garden hose and you turn the water on, the water passing through the garden hose is the DNA being read sequentially to produce a protein. If you have a bend or kink in the hose it will affect the strength of the stream of the water that comes out."

CANCER (Inflammation, Epigenetics, Cancer and Ayurveda): Cancer is the second most common cause of death and accounts for nearly 1 of every 4 deaths there. The World Health Organization estimates that, worldwide, there were 14 million new cancer cases and 8.2 million cancer-related deaths in 2015. It is expected that annual worldwide cancer cases will rise from 14 million in 2015 to 22 million by 2030. This is despite the fact that there is a clear link between lifestyle and cancer prevention. An estimated one third of the most common cancers can be prevented through consumption of a primarily plant-based diet, minimizing chronic inflammation, stress-management strategies, maintaining a healthy weight (BMI), and regular physical exercise. Cancer is described as occurring in three stages: initiation, promotion, and progression. Initiation is thought to often involve a primary mutation in the DNA leading to a cell with increased potential for growth but still dependent on additional genotypic and epigenetic changes to achieve complete transformation to malignancy. Often, if these co-required epigenetic changes do not occur, the mutation will not manifest into cancer. Epigenetic processes may also be involved in cancer initiation. It is possible that epigenetic change may lead directly to cancer initiation. Alternatively, changes already induced within the epigenome may 'prime' cells in such a way as to promote cellular transformation upon a subsequent DNA mutagenic event. In this case the epigenetic component of the cancer initiation is intricately entwined with the genetic component.

The modifications that occur on histone N-terminal tails and on DNA are shown together with the enzymes that lay down and remove the marks. Deregulation of any of these enzymes has the potential to be oncogenic. Frequently, initiation is generated by genotoxic carcinogens that directly damage DNA, while promotion involves the activation and clonal proliferation of initiated cells possibly also by an epigenetic mechanism. Progression is the development of that early cancerous clone of cells into a fully malignant phenotype via both further genetic and epigenetic mechanisms. Malignant cells have minimal requirements for growth factors and are

relatively resistant to normal growth regulation and apoptosis, resulting in uncontrolled growth that is the sine qua non of cancer. The Charaka and Sushrutasamhitas, two well-known Ayurvedic compendiums, described two related categories of swellings, one inflammatory (*Arbuda*) and the other non-inflammatory (*Granthi*), though this division is somewhat indefinite. *Arbuda* is considered to be the more malignant form of the two, corresponding to our modern word “cancer”. There are suggestions in the ancient Ayurvedic medical texts that *Arbuda* is a secondary outcome of a chronic inflammatory pathology. For example, *Arbuda* and *Granthi* come under the category of diseases called “*Sopha*”. *Sopha* can be loosely translated as an “inflammatory swelling. Sushruta was very lucid in his description of *Arbuda*: “The disturbed *Doshas* established in any part of the body afflict the *Mamsa* dhatu and produce a swelling which is fixed, hardened, only slightly painful, circular, broad-based, slowly growing and does not suppurate. This is perhaps an indication that *Sopha*, especially when it persists in chronic form, predisposes the individual to develop *Arbuda*. In Charaka’s narrative on the treatment of *Vātarakta* (gouty arthritis), a chronic inflammatory disease affecting the joints of the body, *Arbuda* is described as sometimes occurring as a complication.

environment and lifestyle. The lifestyle factors include cigarette smoking, diet (fried foods, red meat), alcohol, sun exposure, environmental pollutants, infections, stress, obesity, and physical inactivity. The evidence indicates that of all cancer-related deaths, almost 25–30% are due to tobacco, as many as 30–35% are linked to diet, about 15–20% are due to infections, and the remaining percentage are due to other factors like radiation, stress, physical activity, environmental pollutants etc. .Therefore, cancer prevention requires smoking cessation, increased ingestion of fruits and vegetables, moderate use of alcohol, caloric restriction, exercise, avoidance of direct exposure to sunlight, minimal meat consumption, use of whole grains, use of vaccinations, and regular check-ups.

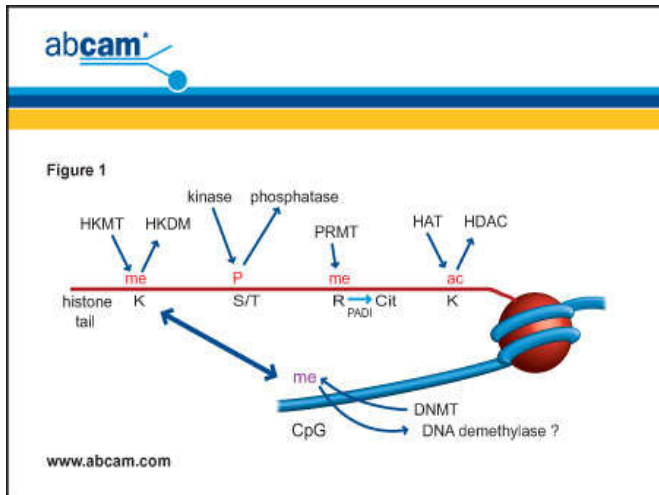


Fig. 1.

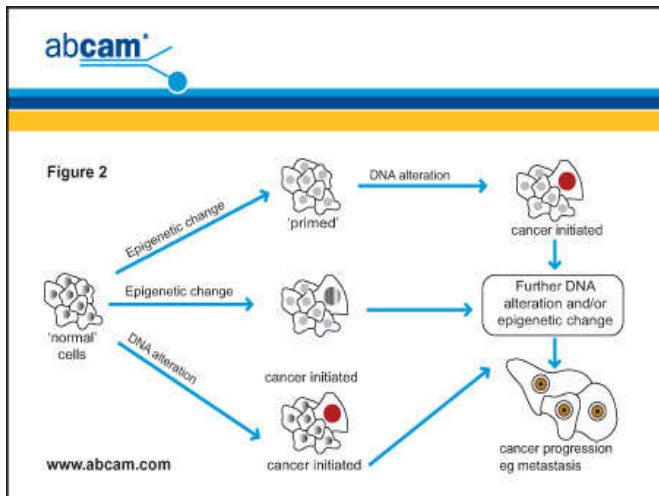


Fig. 2.

Epigenetics and Cancer preventive aspect

Only 5–10% of all cancer cases can be attributed to genetic defects, whereas the remaining 90–95% have their roots in the

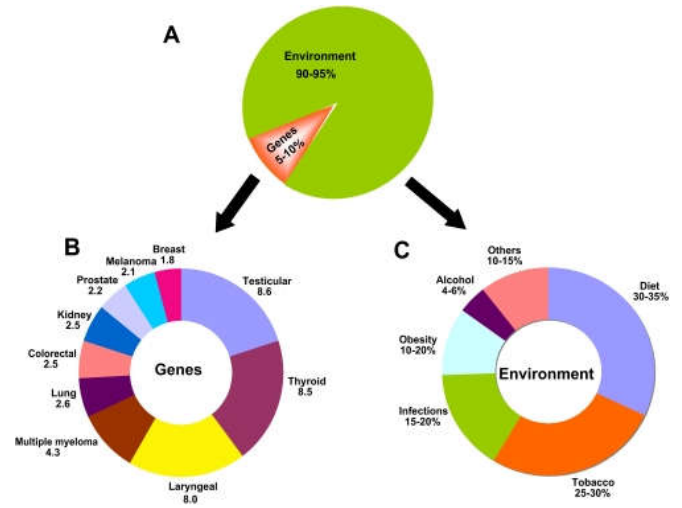


Fig. 3.

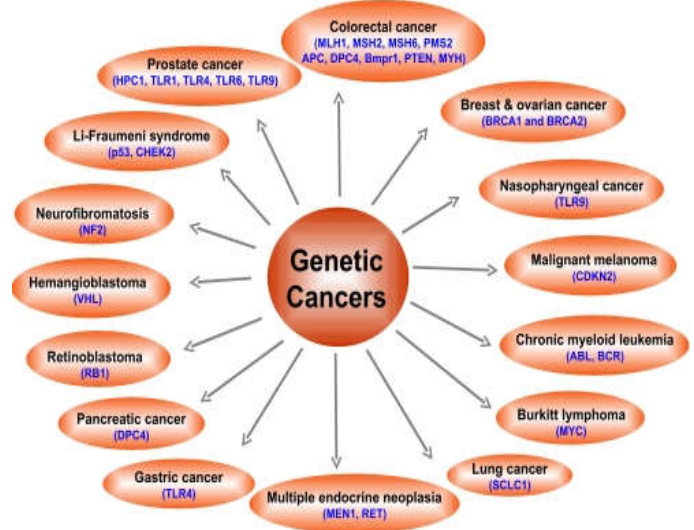


Fig. 4.

These observations indicate that most cancers are not of hereditary origin and that lifestyle factors, such as dietary habits, smoking, alcohol consumption, and infections, have a profound influence on their development. The majority of changes in the genome involve loss of methylation affecting CpG sites (cytosine-phosphate-guanine) which were previously methylated. The presence of these methyl groups usually creates a DNA conformation which blocks access to certain genes and renders them “silent”.

Since thousands of genes are normally epigenetically silenced in every differentiated cell type, the unintended activation of these genes due to de-methylation often increases unwanted gene expression. It should be noted, though, that the hyper-methylation of other genes is the cause of unwanted effects.

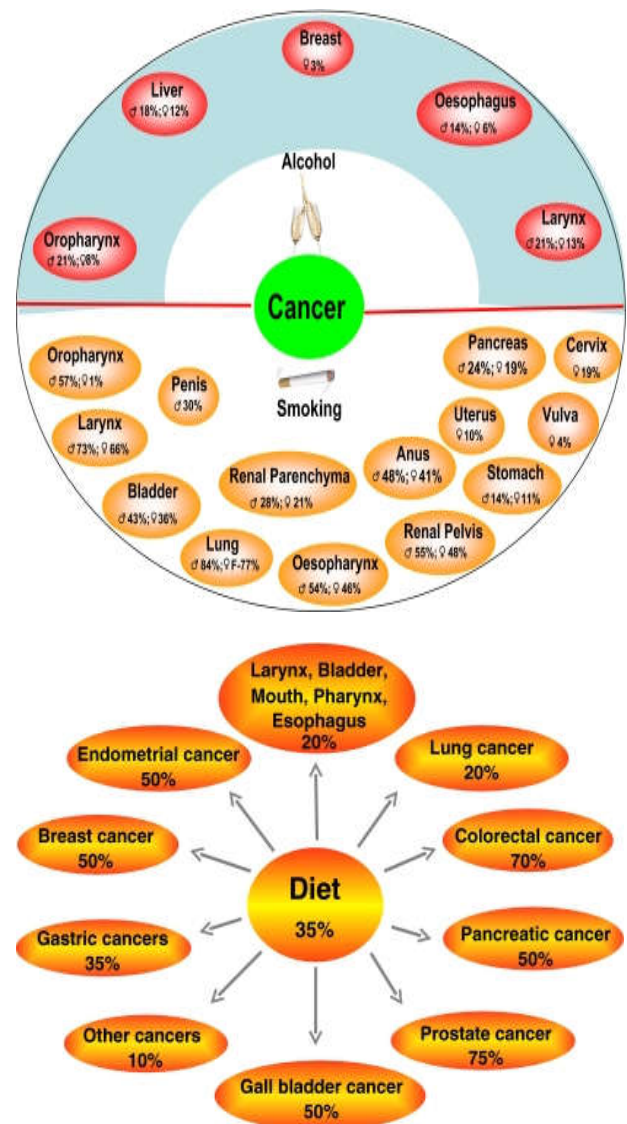
A number of studies suggest that DNA methylation and other persisting epigenetic changes to both DNA and chromatin induce differentiated direct cells back into a “stem-cell like” state predisposing to cancer, partly explaining a higher risk of carcinogenesis in older people or those chronically exposed to toxic agents.

Dietary constituents, by affecting the DNA methylation status, no doubt positively or negatively affect disease risk and progression and probably also the aging process. There are dietary enzyme co-factors such as folate and vitamins B12 and B6, as well as methyl group donors such as methionine (nuts, beef, lamb, cheese, fish, oats, soy, eggs, and legumes), choline (eggs, dairy, nuts, legumes cauliflower, broccoli, cabbage bok choy), betaine (wheat, shellfish, spinach, and sugar beets) and serine (soy, eggs, lentils, nuts, seeds) that increase methylation, and selenium (brazil nuts, oysters, fish, whole wheat, chia seeds, sesame seeds, flaxseeds, barley, rye, oats, beef) green tea polyphenols and bioflavonoids (e.g. epigallocatechin-3-gallate, genistein, ellagic acid, quercetin and hesperidin) that reduce methylation. Although the hereditary factors cannot be modified, the lifestyle and environmental factors are potentially modifiable. The lesser hereditary influence of cancer and the modifiable nature of the environmental factors point to the preventability of cancer. The important lifestyle factors that affect the incidence and mortality of cancer include tobacco, alcohol, diet, obesity, infectious agents, environmental pollutants, and radiation. *Ayurveda* gives us a very straightforward and intuitive approach to healthy eating which emphasizes freshness, moderation, variation and including the six tastes. Proper cooking methods will help “pre-digest” most foods; about 20% of foods should be raw. Lovingly prepared, slowly eaten foods enjoyed in a relaxed setting will no doubt lead to better epigenetic health.

Epigenetics and Cancer curative Aspect

Western medicine is extremely good at treating acute issues and highly technological support such as joint replacement. But the leading causes of mortality in the world are directly related to issues of non-harmonious lifestyle, poor nutrition and stress. Modern medicine treats the symptom of the underlying ailment whereas *Ayurveda* is treating the root of the imbalance. *Ayurveda* analyzes the person with relation to their mind as well as their physical body to determine the correct treatment of the imbalance. This imbalance is not a factor of changing DNA rather an epigenetic factor that can be modified in relation to the patient’s actions and environment. The Charaka Samhita states that disease starts in the mind.” The body and the mind cause substrata of disease and happiness (i.e. positive health). Balanced utilization (time, mental faculties, and object of sense organs) is the cause of happiness.” Today, we know that chronic inflammation may be a causative factor in a variety of cancers. In general, the longer the inflammation persists, the higher the risk of cancer. Hence, acute inflammation, such as occurs in response to a transient trauma or infection, is not a risk factor for the development of neoplasia, though many of the same molecular mediators are generated in both acute and chronic

inflammation. In general, inflammatory leukocytes such as neutrophils, lymphocytes, monocytes, macrophages, and eosinophils provide the substances that are thought to mediate the development of inflammation-associated cancer, although other cells also contribute, including the altered pre-cancerous cells themselves.



Inflammatory mediators include among others: tumor necrosis factor, nitric oxide, adhesion molecules, derivatives of arachidonic acid (prostaglandins, leukotrienes), cytokines, chemokines, and free radicals. Chronic exposure to these mediators leads to increased cell proliferation, mutagenesis, epigenetic modifications, oncogene activation, and angiogenesis. The ultimate result is the proliferation of cells that have escaped normal growth control. Recently there has been evidence from animal models (i.e. mice, zebrafish) that chronic inflammation can promote cancer and possible insights into the mechanisms involved. Those mechanisms involve activation of inflammatory signal pathways such as the NF- κ B signal pathway, signal transducer and activator of transcription 3 (STAT-3), and hypoxia-inducible factor 1 α (HIF-1 α). These substances cause the release of inflammatory mediators such as the proinflammatory cytokines (e.g. TNF and IL-1 β) and proinflammatory enzymes that mediate production of prostaglandins (e.g. COX-2) and leukotrienes (e.g. lipoxygenase), together with expression of adhesion molecules and matrix metalloproteinases (MMPs). This

cascade of events can lead to chronic inflammatory diseases such as arthritis, atherosclerosis, inflammatory bowel disease, chronic sinusitis, or even cancer. In particular, NF- κ B (nuclear factor kappa-light-chain-enhancer of activated B cells) is a type of transcription factor central to the production of chronic inflammation. Transcription factors bind to regions of DNA just adjacent to the genes that they regulate. Depending on the transcription factor, the transcription of the adjacent gene is either up- or down-regulated. NF- κ B is a protein complex that controls the transcription of DNA to messenger RNA, cytokine production and cell survival. NF- κ B is found in almost all animal cell types and is involved in cellular responses to stimuli such as stress, cytokines, free radicals, ultraviolet irradiation, oxidized LDL, and bacterial or viral antigens. Incorrect regulation of NF- κ B has been linked to cancer, inflammatory, and autoimmune diseases, septic shock, viral infection, and improper immune development. NF- κ B, which in essence is a gene regulator (i.e. transcription factor), is itself regulated by its own genes. NF- κ B is a protein composed of two protein subunits, p50 and p52; the creation of these subunits is regulated by two specific genes NFKB1 and NFKB2, respectively. Both p50 and p52 subunits are required to make a NF- κ B protein.

Whereas the production of p50 is an ongoing (“constitutive”) process, p52 production is a tightly controlled process regulated by its gene, NFKB2. In theory, any epigenetic factor which could inhibit or diminish the activity of either the NFKB1 or NFKB2 genes, could effectively block production of NF- κ B, resulting in an anti-inflammatory phenotype (effect). Interestingly, the potent antitumor effects of phytochemicals, such as curcumin, from turmeric, attributed to its anti-inflammatory activities. It inhibits inflammation at least in part by suppressing the transcriptional activity of NF- κ B. Epigenetic marks are, in effect, additional ways of storing information and regulating gene expression. Still there is no idea how these epigenetic modifications are passed on in cell division over many generations. It is not known that although these modifications appear to be very stable, they can be affected by many factors including diet, chemicals, environment, pathological conditions, and even mental state. Inflammation in some way contributes to the initiation and development of cancer but the molecular mechanistic aspects of this phenomenon are not clearly understood. One model that links inflammation to the oncogenic transformation based on a positive feedback loop mechanism involving NF- κ B, RNA-binding protein Lin-28, let-7 microRNA, and IL-6 cytokine. It is likely that epigenetic factors play a major role in any such mechanism.

Conclusion and future perspectives

The phenotype of an individual is the result of complex geneenvironment interactions in the current, past and ancestral environment, leading to lifelong remodeling of our epigenomes. In recent years, several studies have demonstrated that disruption of epigenetic mechanisms can alter immune function and contribute to various cancers. Various replication-dependent and -independent epigenetic mechanisms are involved in developmental programming, lifelong recording of environmental changes and transmitting transgenerational effects. It is likely that understanding and manipulating the epigenome, a potentially reversible source of biological variation, has great potential in chemo-prevention or stabilization of cancer. Much attention is currently focusing on

modulating hyper/hypomethylation of key inflammatory genes by dietary factors as an effective approach to cure or protect against cancer-inflammation. After sequencing his own genome, pioneer genomic researcher Craig Venter remarked at a leadership for the twenty-first century conference, “Human biology is actually far more complicated than we imagine. Everybody talks about the genes that they received from their mother and father, for this trait or the other. But in reality, those genes have very little impact on life outcomes. Our biology is way too complicated for that and deals with hundreds of thousands of independent factors. Genes are absolutely not our fate. They can give us useful information about the increased risk of a disease, but in most cases, they will not determine the actual cause of the disease, or the actual incidence of somebody getting it. Most biology will come from the complex interaction of all the proteins and cells working with environmental factors, not driven directly by the genetic code” Epigenetics has been around 20 years. Ayurveda has been around 5000 years. Both have come to very similar conclusions. Epigenetic research confirms traditional ancient knowledge that diet, lifestyle and mindfulness can all be used to fight disease and promote health. We are here on this planet to optimize the expression of our genes in a way that supports evolution and growth both individually and collectively. “Expression” is the operative word in epigenetic possibility. Genes will take multiple generations before any minor mutations can take place but the expression of our genes can change almost daily.

Our health is a vast spectrum of possibility. “Expression” is the operative word in epigenetic possibility. Our health is a vast spectrum of possibility. Our choices affect our outcomes. We are what we eat. We are not a product of circumstance by which we sit around and watch while our health and happiness deteriorate as we age. We are truly masters of our own demise. The great English poet William Henley summed things It matters not how strait the gate, how charged with punishments the scroll, I am the master of my fate: I am the captain of my soul. Lifelong remodeling of our epigenome is possible. Fruits, vegetables, teas, spices, and medicinal herbs have components that can regulate multiple cancer and inflammatory pathways via epigenetics. Drugs that target a single gene product are unlikely to be of use in preventing or treating cancer. Cancers have long latency periods, we need safe and effective multi-functional treatments that act on entire networks in the body. Bioactive components in food may prevent or treat metabolic diseases via epigenetics. Curcumin, sulforaphane, diindolylmethane (DIM), Indol-3-carbinol (I3C), Phenethyl isothiocyanate (PEITC), Epigallocatechin-3-gallate (EGCG), genistein, quercetin, resveratrol, ellagitannins, butyrate, organosulfur compounds, lycopene. The future of epigenetics is individualized therapies. Western medical approach – develop new drugs which target specific epigenetic components. Recognizes that diet, lifestyle and the environment can have epigenetic effects. Therapy may include drugs with epigenetic targets: DNA-MT inhibitors, HDAC inhibitors, etc. *Ayurvedic* approach – treatments are individualized for each person. Complementary roles of body, mind, and spirit in maintaining health are recognized. Treatment may include changes in diet and/or lifestyle, as well as medicinal herbs and panchakarma therapies. Medications are chosen based on their unique characteristics (Rasa, *Guna*, *Virya*, *Vipaka*, and *Prabhava*) and the *Prakriti* and *Vikriti* of the person being treated. Mind, body, and spirit are the pillars of health and together determine whether a person is

experiencing health or is susceptible to disease. Disease can occur from imbalances in any of these three pillars. "Every individual is different from another and hence should be considered as a different entity. As many variations as there are in the universe, all are seen in human beings" –Charaka Samhita.

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