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Oncoepigenomics and Oncoecogenomics: Personalizing the Cancer Treatment

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Abstract

The vast majority of cancer cases are due to environmental risk factors, many of which (but not all) being controllable lifestyle choices and thus preventable. It has been suggested that more than 30% of cancer deaths could be prevented by avoiding risk factors including: tobacco, overweight, obesity, insufficient or/and inappropriate diet, physical inactivity, alcohol, transmitted infections, and air and water pollution. However, not all environmental causes are controllable such as naturally occurring background electromagnetic radiation. This article is concerned with those cancers that are due to epigenetics and ecogenetics and their oncogenomic treatments (which I shall refer to as oncoepigenomics and oncoecogenomics, respectively). Analyzing the epigenomics and ecogenomics of cancer, actionable treatment indicators are identified and recommended for personalizing cancer treatment.

Keywords: Epimutations; Immunotherapy; Oncoecogenomics; Oncoepigenomics; Oncogenomics; Reverse transcriptome; Transcriptome.

Abbreviations: AD: Alzheimer Disease; ALS: Amytrophic Lateral Sclerosis; ATI: Actionable Treatment Indicators; CAR: Chimeric Antigen Receptors; ChiP: Chromatin Immuno Precipitation; CNV: Copy Number Variants; DNAMT: DNA Methyl Transferase; ecoATI: Ecogenetic Actionable Treatment Indicators; EGP: Environmental Genome Project; epiATI: Epigenetic Actionable Treatment Indicators; GE: Gene-Environment (interactions); GGE: Gene-Gene-Environment (interactions); HAT: Histone Acetyl Transferase; HCGP: Human Cancer Genome Project; HDAT: Histone DeACetylase Transferease; HGP: Human Genome Project; HLMT: Histone Lysine Methyl Transferase; MLL: Mixed Lineage Leukemia; NIEHS: National Institute of Environmental Health Sciences; PAMT: Protein Arginine Methyl Transferase; PCR: Polymerase Chain Reaction; PD: Programmed Death; PD: Parkinson Diseae; qPCR: Quantitative PCR; T2D: Type 2 Diabetes; TF: Transcription Factors; TPG: Tumor Promoter Genes; TSG: Tumor Suppressor Genes

Diseases Listed

Alzheimer; Amyotrophic lateral sclerosis; Cancer (breast, cervical, colorectal, head and neck, leukemia, ovarian, prostate, sarcoma); Cardiovascular; Diabetes; HIV/AIDS; Infectious diseases; Leukemia (acute myeloblastic, acute myeloid); Lymphoma (Burkitt); Malaria

Drugs cited: Varinostat (A histone deacetylase inhibitor)

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Introduction

In an earlier companion article, I heralded the coming of age of oncogenomics, a personalized cancer therapy [1]. That approach proceeds from a scanning of the genome of each individual patient for "actionable treatment indicators" (ATI). It uses this information to apply well-known treatment approaches (e.g., synthetic chimeric antigen receptor CAR- and Programmed Death PD - immunotherapy, antiangiogenesis, etc.) that had heretofore been applied generally with little personalization to the patient under treatment. We are still at the initial stage where the genome is scanned for copy number variants (CNVs). I also recommended further steps to investigate other genomic information sources including the transcriptome, the reverse transcriptome, and known processes and mechanisms of genetic changes (Table 1). While oncogenomics is time and resource prohibitive, the process could and should be accelerated.

With the deeper understanding of cell biology and genetics, it now appears that cancer is less an organ disease and more a disease of molecular mechanisms caused by mutations of specific genes [2]. It is fundamentally a disease of tissue growth regulation failure when the genes that regulate cell growth and differentiation are altered. Most cancers have multiple possible concurring causes, and it is not possible to prevent all such causes. However, only a small minority of cancers (5-10%) are due to inherited genetic mutations whereas the vast majority (90-95%) are non-hereditary epigenetic [3]. And ecogenetic mutations that are caused by various agents (environmental factors, physical factors, and hormones). Thus, although there are some genetic predispositions in a small fraction of cancers, the major fraction is due to a set of new genetic mutations (the "epigenetic and ecogenetic" mutations). The aim of this article is to expand oncogenomics to the broader field of oncoepigenomics and oncoecogenomics. But, let is start with a comparison of these three inter-related disciplines to be followed by a primer on cancer epigenetics [4].

Genetics Versus Epigenetics and Ecogenetics

It is of interest to contrast, at least in part, genetics with epigenetics and ecogenetics. This is the tentative purpose of Table 1 below:

Property	Genetics	Epigenetics	Ecogenetics
Type of study	o Genes and heredity o Genetic variations in living organisms (bacteria, plants, animals, humans) o Relationship with biochemistry and molecular biology	o Cellular and physiological traits inherited by daughter cells but *not* caused by DNA changes o Relevant changes to the genome that do not involve a change in the nucleotide sequence	o Genes-environment and genes-genes-environment interactions
Characteristic		Can be divided into "predetermined" and "probabilistic" epigenesis	
Processes	o Gene linkage o Gene regulation o Gene mutation o Replication o Duplication o Inversion o Deletions o Chromosomal cross-over o Chromosomal translocation	o Genetic drift o Genomic imprinting o Transgenerational inheritance o Bookmarking o Carcinogenesis progress o Cloning limitations o Gene silencing o Heterochromatin o Histone modifications regulations o Imprinting o Maternal effects o Paramutation o Pathogenesis limitations	o Family history ecogenetics o Infectious diseases (malaria; HIV/AIDS) o Neuro degenerative diseases (Alzheimer, Parkinson, Amyotrophic Lateral Sclerosis aka *Lou Gehring disease*), cardiovascular diseases, Type 2 diabetes)

		o Position effect o Reprogramming o Teratogen effects o Transvection o X-chromosome inactivation	
Mechanisms	o Frequency-Effect relationship o Linkage disequilibrium	o DNA methylation (also applies to RNA Epigenetics) o Histone modification (acetylation, citrillination, methylation, phosphorylation, ribosylation, summoylation, ubiquitylation) o Chromatin remodeling (post-translational modifications of amino-acids that make up histone proteins, addition of methyl groups to DNA)	o Biotransformation enzymes' role in processing toxic substances (repair of damaged DNA: endogenous, exogenous;; xenobiotic metabolism and disease risk) o Non-functional DNA repair systems causing diseases
Control		Through action of repressor genes that attach to silencer regions of DNA	
Agents		o Prions o RNA o Micro-RNA	o Infectious diseases o Pharmaceutical agents o Metabolism o Diet and nutrition o Foodstuffs o Food supplements o Environmental/chemical agents o Physical agents o Lifestyle and behavioral agents
Changes	o Genetic variations	o Last through cell divisions for duration of the cell's life o Can be transferred to next generations o Can modify action of certain genes (not DNA) o Can be caused by DNA changes and by food/diet	
Inheritance	Inheritance theories: o Mendel's single gene o Laws of discrete inheritance o Law of segregation o Law of independent assortment for multiple genes	o “Cell memory”	

Applications	o Evolution o Nature *and* Nurture	o Evolution o Cancer o Teratogen effects o Cardiovascular diseases o etc.	o Vaccination o Microbial fermentation o Pasteurization o Disease prevention o Clinical medicine
Functional	o Molecular basis of inheritance o Natural selection	o Engineered Epigenome	Causative agents for tuberculosis, cholera, anthrax
Linkages			o Organisms to specific diseases o Diseases due to environmental exposure o Some food components and drugs to abnormal reactions because of specific hereditary susceptibility o Rare adverse reactions to standard drug dose that required the breakdown of certain enzymes o Adverse response to anti-malarial drug (*primaquine*) because of inherited X-chromosome recessive trait caused by G6PD deficiency o Hemolytic anemia caused by *primaquine* o Exposure to any kind of environmental and xenobiotic (chemical) agents

Table 1: Comparison between Genetics, Epigenetics and Ecogenetics.

The several epigenetic and ecogenetic processes and mechanisms listed in Table 1 provide tools that will be helpful in the development and implementation of oncoepigenomics and oncoecogenomics.

The Epigenetics of Cancer

In the earlier companion publication, I had discussed the genetics of cancer including the nature of cancer as a disease of tissue growth regulation failure resulting from the imbalance between tumor promoter genes (TPG) (or oncogenes) and tumor suppressor genes (TSG) that inhibit cell division and survival [5]. Malignant transformation can occur through the formation of new oncogenes, the inappropriate over-expression of normal oncogenes, or else by the under-expression or disabling of TSG. Typically, changes in many genes are required to transform a normal cell into a cancer cell. Genetic changes can occur at different levels and by different mechanisms, more commonly through mutations or changes in the nucleotide sequence of genomic DNA such that large-scale mutations involve the deletion or gain of a portion of a chromosome [6]. If the error control processes fail, then the mutations will survive and be passed along to daughter cells. Other genomic processes were also briefly reviewed (including amplification, translocation, point mutations, deletions, and insertions, disruption, and replication). I also discussed the transformative, self-amplifying and compounding processes of a normal cell into cancer, how cancer becomes resistant and how understanding the biological underpinnings could help fight this resistance, developing a new biomarker for testing the sensitivity of a patient to specific drugs and even a diagnostic test, thereby assessing the benefit of a specific drug treatment to a given patient prior to initiating treatment [7].

Beyond genetics, I am here interested in cancer epigenetics and ecogenetics of which I shall provide brief primers. The mechanisms and endpoints of epigenetics are illustrated in Figure 1 and discussed thereafter.

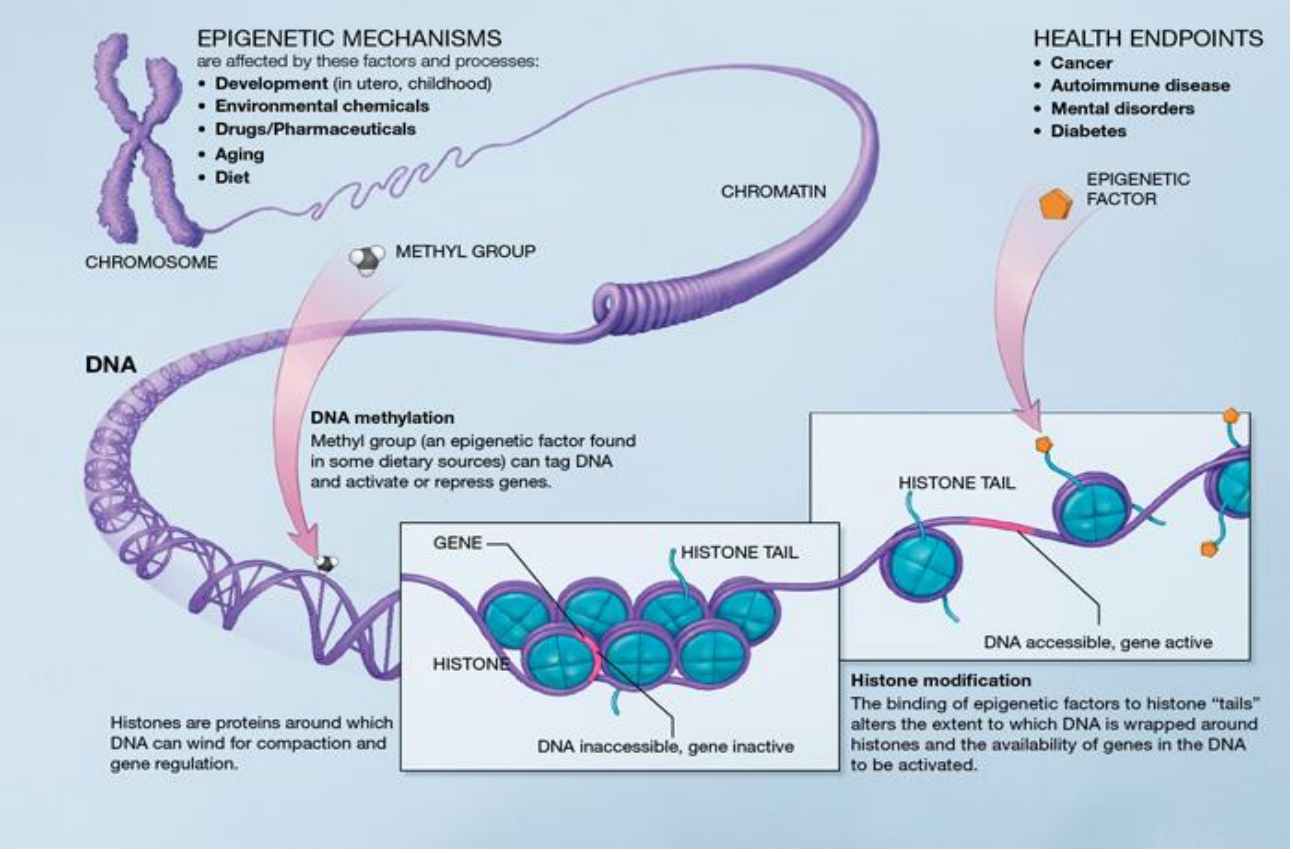

Figure 1: Mechanisms and Health Endpoints of Epigenetics.
Source: U.S. National Institutes of Health

Epimutations as the Cause of Genetic Instability Characteristic of Cancer

Cancer epigenetics is the study of epigenetic modifications to the genome of cancer cells that do not involve a change in the nucleotide sequence. Epigenetic alterations are as important as genetic mutations in the transformative processes of a normal cell into cancer. Such alterations include the silencing of tumor suppressor genes (TSG) and the activation of tumor promoter genes (TPG, or oncogenes) by altered CPG island methylation patterns, histone modifications, chromatin remodeling, and dysregulation of DNA binding proteins. Whereas cancer has been viewed as a set of diseases that are driven by progressive genetic abnormalities (mutations in oncogenes, TSGs, and chromosomal abnormalities), it is also driven by epigenetic alterations (changes in DNA methylation: hyper- and hypo-methylation; histone modifications; and changes in chromosomal architecture caused by inappropriate expression of proteins). These changes may remain through cell divisions, last for multiple generations, and can be considered to be "epimutations" (equivalent to mutations) [8]. They occur early in the progression to cancer and likely cause the genetic instability characteristic of cancers. The epigenetic deficiencies in expression of DNA repair genes, in particular, likely cause an increased frequency of mutations, some of which then occur in oncogenes and TSGs. Epigenetics has the potential to explain mechanisms of aging, human development, heart disease, mental illness, and for special interest here the origins of cancer (as well as several other conditions). Some investigators even think that epigenetics may ultimately turn out to have a greater role in disease than genetics [9].

Epigenetics of DNA Repair

Epigenetic reductions in the expression of DNA repair genes are very frequent in sporadic (non-germ line) cancers, as shown among the representative cancers illustrated in Table 2, while mutations in DNA repair genes in sporadic cancer are very rare. Deficiencies in expression of DNA repair genes cause increased mutation rates and genome instability, which is likely the main

underlying cause of the genetic alterations leading to cancer [10]. In fact, the first event in many sporadic neoplasias is a heritable alteration that affects genetic instability; also, epigenetic defects in DNA repair are somatically heritable.

Cancer	Gene	Frequency	Cancer	Gene	Frequency
Breast	BRCA1	13%	**Ovarian**	WRN	36%
	WRN	17%		BRCA1	5-30%
				FANCF	21%
				RAD51C	3%
Colorectal	MGMT	40-90%	**Head & Neck**	MGMT	35%-57%
	WRN	38%		MLH1	27%-33%
	MLH1	2%-65%		NEIL1	62%
	MSH2	13%		FANCB	46%
	ERCC1	100%		MSH4	46%
	Xpf	55%		ATM	25%

Table 2: Frequency of Epigenetic Changes (CpG Island Methylation) in DNA Repair Genes in Sporadic Cancers.

Epigenetic Carcinogens

A variety of toxic compounds or pathogens (diethylstilbestrol, arsenite, hexachlorobenzene, nickel) are considered as epigenetic carcinogens in that they increase the incidence of tumors. However, they do not show mutagen activity. By epigenetic mechanisms, many teratogens (such as diethylstilbestrol) exert specific effects on the fetus and throughout the life of an affected child. However, the possibility of birth defects resulting from the child's parents and their parents' exposures have not been observed although a range of male-mediated abnormalities have been demonstrated. Recent studies have shown that the mixed lineage leukemia (MLL) gene causes leukemia by rearranging and fusing with other genes in different chromosomes, which is a process under epigenetic control. Other investigations have concluded that alterations in histone acetylation and DNA methylation occur in various genes influencing prostate cancer [11]. Gene expression in the prostate can be modulated by nutrition and lifestyle changes. Figure 2 illustrates epigenetic patterns in normanl and cancer cells. The Figure is separated into two parts for a normal cell: an inaccessible heterochromatin part and an accessible euchromatin [12].

In the first part: Figure 2(A1) shows a repetitive sequence of a methylated CpG site in which transcription does not take place whereas Figure 2(A2) shows the hypometylation of DNA in a repetitive sequence with allowed transcription. In Figure 2(B1) for a normal cell, histone modifications are illustrated in a closed chromatin configuration with no transcription allowed whereas Figure 2(B2) shows the same for a cancerous cell with loss of histone methylation and allowed transcription [13]. In the second part, Figure 2(C1) shows a normal cell with umethylated CpG island and methylated gene body with initial transcription before exon 1 but no transscriptions thereafter at the exons 1, 2 or 3 illustrated whereas, for a cancer cell, Figure 2(C2) illustrates hypermethylation of a promoter with the opposite transcription pattern. Lastly, Figure 2(D1) for a normal cell shows histone modifications in an open chromatin modification with transcription whereas, for a cancer cell, Figure 2(D2) shows the .loss of histone acetylation with the absence of transxcription.

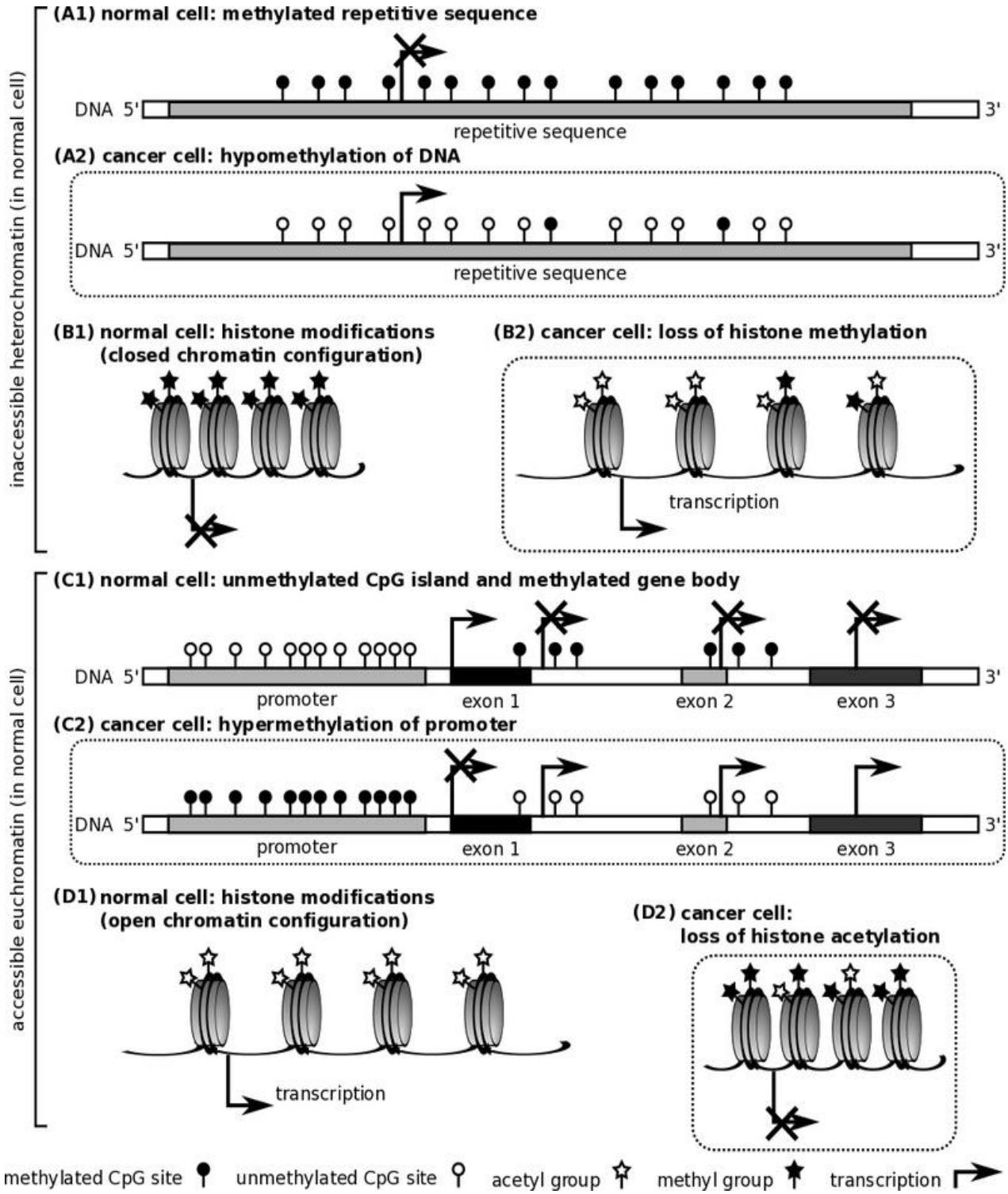

Figure 2: Epigenetic Patterns in Normal and Cancer Cells.

Drug development has focused mainly on Histone Acetyl Transferase (HAT) and Histone DeACetylase (HDAC), and has included the introduction to the market of the new pharmaceutical Varinostat, an HDAC inhibitor. HDAC has

been shown to play an integral role in the progression of oral squamous cancer. Current front-runner candidates for new drug targets are Histone Lysine Methyl Transferase (HLMT) and Protein Arginine Methyl Transferase (PAMT). Applications of epigenetics to cancer sub-types (cervical, leukemia, prostate, sarcoma, etc.) will not be discussed here. More epigenetic aspects remain to be discussed such as functional epigenomics (or the engineering of the epigenome), RNA and beyond RNA-epigenetics [14]. Such a discussion would go far beyond the scope of this article and will not likewise be presented here.

The Ecogenetics of Cancer

Ecogenetics is concerned with the identification of "polymorphisms" in genes involved in environmentally-induced diseases, specifically cancer for our present purpose. Ever since the origin of DNA-based life, genomes have been subjected to environmental stresses. Every second, the genome of each of our cells is altered, broken, and reassembled. The survival of cells, humans, and species depends on mechanisms to repair this damage and reconstitute genomes. Evolution has been at work for billions of years to produce exquisite DNA repair systems that patrol the genome, fixing or replacing damaged, altered, and miscoded nucleotides [15]. The ability of the cell to maintain its genetic integrity is crucial for, without this ability, there would ensue a cascade of mutations reaching an error threshold at which point the genetic information could no longer be maintained. In order to correct this damage before it affects cellular functionality or triggers apoptosis, the cell has evolved multiple repair mechanisms (reversal of damage, base excision repair, nucleotide excision repair, mismatch repair, recombination with restoration of DNA sequences, and bypass of lesions by special DNA polymerases).

Genetic variations in the human population can affect the efficiency and accuracy of these repair mechanisms and can lead to greater disease susceptibility. Unrepaired DNA damage can reduce the overall fitness of a cell, triggering cell cycle arrest, apoptosis, unchecked growth, or other diminished functionality [16]. Therefore, loss of any of these repair pathways in humans can result in mutations, cancer and death. Variability in the ability of these repair systems to perform may ultimately lead to an increase in mutations in somatic cells (any cells that are not egg or sperm) and to a higher risk for disease. Polymorphisms in DNA repair enzymes may increase the risk of disease [17].

Environmental Agents with Known Ecogenetic Variation

In 1997, as part of the Human Genome Project (HGP), the (U.S.) National Institute of Environmental Health Sciences (NIEHS) started the Environmental Genome Project (EGP)--a comprehensive effort to identify "polymorphisms" in genes involved in environmentally-induced diseases. The key objective is to identify alleles that confer susceptibility to the adverse effects of environmental agents [18]. Classes of environmental agents with known ecogenetic variation have been summarized in Table 3.

Class of Agent	Nature of Effect	Ecogenetic Factors
1. INFECTIOUS DISEASES	o Infections, autoimmune disorders, malaria, ankylosing spondylitis o Metabolic disorders	o Defects in cellular or humoral immunity, HbS, G6PD, thalassemia, HLA-B27 o Metabolic problems
2. PHARMACEUTICAL AGENTS	o Biotransformation o Target site susceptibility o Toxicity from chemotherapy	o Acetylation, CYP variants o G6PD deficiency o Thiopurine methyltransferase
3. METABOLISM	o Metabolic disorders	
4. DIET & NUTRITION	o Malnutrition o Lactose intolerance o Favism o Hyperhomocysteinemia o Dyslipidemia o Alcohol sensitivity	o Metabolic problems
5. FOODSTUFFS	o Lactose intolerance	o Intestinal lactase turned off at weaning in

	o Celiac disease o Nuts intolerance o Hemolysis from fava bean ingestion o Atherosclerosis o Thyroid goiter o Nutritional disorders	most humans o Sensitivity to wheat gluten o Allergies (may be fatal) o G6PD deficiency o Hyperlipidemias, hyperhomocysteinemia o Phenylthiocarbamide nontasters o Phenylketonuria, ornithine transcarbamylase deficiency, hypophosphatemic rickets, some rare single gene disorders
6. FOOD SUPPLEMENTS	o Iron deposition diseases o Food additives	o Iron absorption increases hematochromatosis or thalassemia gene
7. ENVIRONMENTAL / CHEMICAL AGENTS: o Inhaled pollutants o Metal poisoning o Pesticides o Occupational exposure (ionizing radiation)	 o Emphysema o **Lung cancer** o **Bladder cancer** o Minamita neurologic disease o Neurotoxicity o X-and higher energy radiation	 o α-1 Antitrypsin deficiency o Arythydrocarbon hydroxilase induction and CYP variants o Nicotine metabolism acetylation differences o Organic mercury ingestion (?) o Paraoxonase (PONI) variation o DNA damage, **cancer** induction
8. PHYSICAL AGENTS	o Tolerance for heat, cold, humidity, motion, sunlight	o Mechanisms unspecified, UV DNA damage repair
9. LIFESTYLE & BEHAVIORAL AGENTS: o Behavior o Stress:	 o Stimulants – Caffeine (wakefulness) o Alcohol (Flushing syndrome) o Drugs of abuse o Metabolic disorders o Smoking o Sexually transmitted infections o Lack of physical exercise	 o Uncertain o Aldehyde dehydrogenase deficiency o Metabolic disorders o **Lung cancer** o HIV/AIDS, syphilis, gonorrhea,

Table 3: Classes of Environmental Agents with Known Ecogenetic Variation.
Source: Adapted and augmented from Ommen and Motulsky (1978), Motulsky (2002, 2006), Lampe and Potter (2006), Saxon (2006).

Of particular note in Table 3 are the effects of environmental/chemical agents such as inhaled pollutants that can induce lung and bladder cancer and likewise for high-energy electromagnetic radiation [19]. Similarly, lifestyle and behavioral agents (such as smoking) can induce lung cancer. In Figure 3, common DNA damaging agents are charted including examples of lesions they cause in DNA, and pathways used to repair these lesions. Also shown are many of the genes in these pathways, an indication of which genes are epigenetically regulated to have reduced (or increased) expression in various cancers. It also shows genes in the error prone microhomology-mediated end joining pathway with increased expression in various cancers [20].

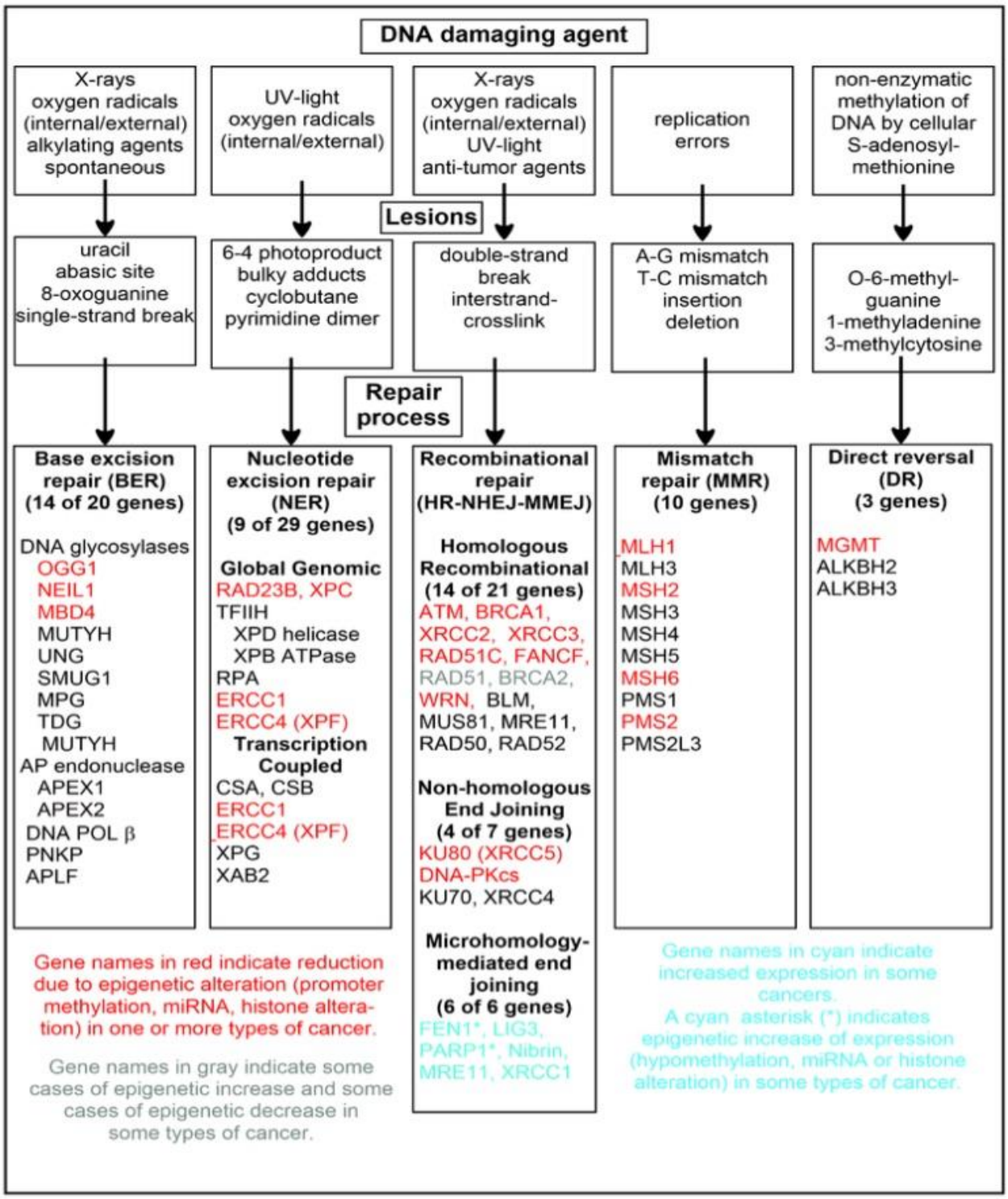

Figure 3: Common DNA Damaging Agents, Legions they Cause and Repair Processes.
Source: Bornstein0275, Wikipedia.

Role of Enzymes in Processing Toxic Substances

A major area of focus in pharmacogenetics and ecogenetics research to date is the role of enzymes in processing toxic substances. There are many enzymes in the body that participate in the metabolism and elimination of endogenous compounds and xenobiotics. These biotransformations usually aid in the ultimate elimination of such compounds, although in some cases the reactions bioactivate parent compounds [21]. Individual differences here can limit their efficacy, or lead to severe adverse reactions. Because of the need to recall several widely utilized drugs due to unexpected severe toxic effects, pharmacogenetic research is now focused toward the definition of individualized therapies that take into account individuals' genetic makeup. In addition, evidence is emerging that these same biotransformation enzymes can also modulate an individual's susceptibility to environmental and occupational toxicants – the specific area of ecogenetics research [22]. The toxic effects of many chemicals result from the ability of the activated chemical to damage DNA. DNA damage from both endogenous and exogenous sources occurs frequently in every living cell in our bodies. Fortunately, our cells possess remarkably efficient repair processes that remove and correct such DNA damage [23].

Exogenous and Endogenous DNA Damage

There are two main categories of DNA damage: exogenous (environmental) and endogenous (internal, spontaneous). With all of this damage occurring within the cell, it is no wonder that drugs that reduce the damage load on cells, such as anti-oxidants, are being promulgated for cancer prevention [24]. Exogenous DNA damage can be caused by many environmental agents, including (a) natural chemicals found in food (e.g., aflatoxins); (b) synthetic (human-made) chemicals (e.g., benzopyrine found in cigarette smoke); and (c) chemicals used in chemotherapy of cancer (e.g., cisplatin); (d) exposure to UV radiation produced naturally by the sun or artificially by tanning booth lamps; and (e) ionizing radiation such as γ-rays and X-rays (during diagnosis and therapeutic treatment; occupational exposure) [25].

The damages result in (a) the chemical instability of DNA, which can manifest as depurination and depyrimidation events resulting in the loss of a base from the DNA strand. It can be estimated that 10,000 bases per cell per day are lost spontaneously and subsequently repaired; and (b) the production of reactive molecules by normal cellular processes. The damage in cells by reactive oxygen (e.g., hydroxyl radicals, superoxide anion) is likewise estimated to be 10,000 events per cell per day [26]. On the other hand, endogenous DNA damage is caused by chemical alterations such as methylation, and incorporation of incorrect bases during DNA synthesis.

Gene-Environment Interaction in the Etiology of Diseases

All the following cancers (lung, gastro-intestinal, and others) [and also neurodegenerative diseases (NDDs) including Alzheimer, AD; Parkinson PD; and amyotrophic lateral sclerosis, ALS or Lou Gehrig disease); cardiovascular diseases (CVDs*);* type 2 T2D diabetes; infectious diseases such as malaria and HIV/AIDS] clearly have a genetic and an environmental component to their etiology [27]. The complexity of the diseases poses substantial difficulties in establishing clear-cut associations. Most often, the end point is the result of an array of multifactorial aspects involving both the individual's genome and the environment. In some instances, gene-environment (GE) interactions must be enlarged to gene-gene-environment interactions (GGE) [28].

Well over 100 types of cancer have been observed to occur in humans, each with its own unique constellation of risk and protective factors. However, no matter how strong a particular risk factor might be, whether an environmental exposure such as tobacco or alcohol, or an inherited predisposition to cancer, it is quite rare that one factor completely determines the development of cancer. Multiple factors must therefore play a role in causing a normal cell to develop the myriad genetic abnormalities characteristic of the malignant phenotype [29]. In some instances, risk factors may act through different biological pathways, and are therefore said to act independently of each other. In other instances, the effect of one risk factor may depend on the presence of another risk factor, that is, they may interact. The interacting risk factors might both be environmental in nature. In other instances, environmental risk factors may interact with genetic factors in modifying disease risk. Finally, multiple gene products typically act in complex metabolic pathways, and they may interact with each other in determining disease risk (e.g., gene-gene interactions). Notwithstanding the wide variation in etiology of different cancers, it is important to consider each tissue or organ system in its own particular context [30].

Oncoepigenetics and Oncoecogenetics

Like for oncogenomics, the approach would be to sequence the epigenome and the ecogenome of the patient in order to evidence epigenetic and ecogenetic

actionable treatment indicators (epiATIs and ecoATIs, respectively) [31].

Actionable treatment indicators in the epigenome

These are:
Gene expression changes in the cancerous tissue: These can be analyzed by quantitative polymerase chain reaction (qPCR) wherein both positive and negative control PCR primer pairs are included to determine the fold enrichment, the latter amplifying a region of the genome not bound by the antibody target of interest. There are commercially available analysis kits (particularly the ones developed by the U.S. Company Active Motif.)

Further, referring to Figure 1, other epiATIs are:

a. Changes in DNA Methylation: as evidenced by methyl groups that have tagged DNA and activated or repressed genes. These can be shown, in particular, by enrichment followed by PCR analysis.
b. Epigenetic factors that bind to histone tails: these alter the extent to which DNA is wrapped around histones, thus dictating the availability of genes in the DNA to be activated
c. Changes in chromatin structure: These can be shown by chromatin immunoprecipitation (ChiP) whose success depends on the quality of the ChiP antibody and the abundance of the target protein. Because it enables identification of the localization of proteins bound to specific DNA loci, ChIP is a powerful tool for studying protein/DNA interactions. Applications include:

i. Transcription factors (TF: these are the regulatory proteins that bind to DNA to either promote or inhibit the transcription of a gene);
ii. Co-regulatory proteins;
iii. Modified histones;
iv. Chromatin-modifying enzymes; and
v. Polymerases.

When used in combination with whole-genome analysis, insights are possible into gene regulation, gene expression, mechanisms of chromatin modification and pathway analysis.

Actionable treatment indicators in the ecogenome

These are the various chemical/environmental agents and the lifestyle & behavioral agents listed in Table 3. A person's likelihood of developing a particular cancer is determined largely by a complex interplay of risk factors involving environmental exposures, lifestyle factors and inherited susceptibility [32]. The challenge is to understand in sufficient detail how these specific factors interact in causing (or preventing) these cancers, so that more effective prevention and early detection programs can be developed and applied toward persons at highest risk of the disease [33]. (Further, let us recall here, this author's admonition that "*risk is not cause, and risk management is not cure, only palliation*".).

Summary and Conclusions

Three types of epigenetic mechanisms have been discussed (a) chromatic remodeling, (b) histone modifications, and (c) DNA methylation. Chromatin remodeling is accomplished through two main mechanisms: post-translational modification of the amino acids that make up histone protein, and addition of methyl groups to the DNA. Although histone modifications occur throughout the entire sequence, mechanisms of heritability of histone state are not well understood. These modifications include: acetylation, citrillination, methylation, phosphorylation, ribosylation, sumoylation, and ubiquitylation. Much is known about the mechanism of heritability of DNA methylation state during cell division and differentiation. Heritability of methylation state depends on certain enzymes, such as the DNA methyltransferase (DNAMT1), that have a higher affinity for 5-methylcytosine than for cytosine. If this enzyme reaches a "hemimethylated" portion of DNA (where 5-methylcytosine is in only one of the two DNA strands) the enzyme will methylate the other half.

DNA methylation patterns are known to be established and modified in response to environmental factors. Its molecular mechanism of inheritance is different from the canonical Watson-Crick base-pairing mechanism. There are various applications of epigenetics in medicine and drug development, of particular importance in cancer and cancer treatment. Epigenetic pharmaceuticals could be a replacement or adjuvant therapy for currently accepted treatment methods such as radiation and chemotherapy, or could enhance the effects of these current treatments. The epigenetic control of the proto-onco regions and the tumor suppressor sequences by conformational changes in histones directly affects the formation and progression of cancer. Epigenetics also has the factor of reversibility, a characteristic that other cancer treatments do not offer. Drug development (e.g., Varinostat) has focused mainly on histone acetyl transferase and histone deacetylase. Current front-runner candidates for new drug targets are histone lysine methyl transferase and protein arginine methyl transferase. The discussions of other drug developments, applications to cancer sub-types, functional epigenomics (or epigenome engineering), and

RNA and beyond RNA-epigenetics remain to be fully investigated in the future.

Research about cancer causes focuses on the following issues: (a) what are the agents (e.g. viruses) and events (e.g. mutations) that cause or facilitate genetic changes in cells destined to become cancerous? (b) What is the precise nature of the genetic damage, and the genes that are affected by it? and (c) what are the consequences of those genetic changes on the biology of the cell, both in generating the defining properties of a cancer cell, and facilitating additional genetic events that lead to further progression of the cancer. In this process, a distinction is tacitly made between solid and non-solid (e.g., blood) tumors. In the former case, immunotherapy with autologous CAR-T cells engineered to target the appropriate cancer cells is employed. Standard DNA tests are conducted to zoom in on specific loci in the cancer cells' genome. Such DNA tests have been useful in identifying "actionable mutations", that is, those that indicate the cells could be vulnerable to a particular drug. The idea of basing cancer treatments on DNA mutations is not new although it can be difficult to sift out "actionable findings" from DNA sequencing data. In non-solid tumors (e.g., myeloma, a blood cancer): autologous CAR-T cells engineered to target RCMA (a protein on the surface of myeloma cells) did not succeed. Research on multiple myeloma has lagged behind solid tumors in trying to implement a personalized approach and incorporating genomics data in the treatment.

Problems with multiple myeloma are multiple in that pathology reports do not identify clearly the drivers of the cancer and DNA sequencing does not always give a clue as to how to manage the cancer. Possible solutions are then RNA sequencing to have a peek not just at gene mutations, but also at other changes in the cancer cells (example: copy number variations, CNVs) that might be treatment-relevant. With the above in mind, we are now searching for all epigenomic and ecogenomic processes and pathways that could evidence actionable treatment indicators utilizing a multi-drug chemotherapeutic tool.

A major challenge in the field of ecogenomics is the correct identification of genetic variation that is biologically meaningful. A major area of focus is the role of enzymes in processing and eliminating toxic substances. These biotransformation enzymes can also modulate an individual's susceptibility to environmental and occupational toxicants, and are responsible for oxidative metabolism and repair of DNA damage. They are important in understanding the various diseases linked to nonfunctional DNA repair systems. The different classes of environmental agents with their known ecogenetic variation, the nature of their effect, and the associated ecogenetic factors have been briefly addressed. The various gene-environment interactions that are important in the etiology of diseases have been reviewed in several cases, especially cancer including breast, lung and gastrointestinal cancer (but they also apply to neurodegenerative diseases including Alzheimer, Parkinson, and amyotrophic lateral sclerosis; cardiovascular disease; type 2 diabetes; and infectious diseases, including malaria and HIV/AIDS). A person's likelihood of developing a particular cancer is determined largely by a complex interplay of risk factors involving environmental exposures, lifestyle factors, and inherited susceptibility. The challenge is to understand in sufficient detail how these specific factors interact in causing (or preventing) these cancers, so that more effective prevention and early detection programs can be developed and applied toward persons at highest risk of the disease. The several actionable treatment indicators in oncogenomics, and more broadly epigenomics and ecogenomics, have been preliminarily identified and it is hoped that clinical trials could be initiated to test their use for the overall purpose of personalizing cancer treatment.

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