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Epigenetic Changes in Aging and Age-related Disease

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Abstract

The epigenome refers to the complete set of heritable chemical modifications made to DNA and histone proteins. Certainly, the most well characterized epigenetic mark is the covalent addition of a methyl group to a CpG dinucleotide site in the genome. The DNA methylome—a collection of methyl marks established during embryogenesis—creates a complex regulatory network involved in cell type differentiation, homeostasis and regulating gene expression in response to environmental stimuli and stress throughout life. Collectively, an increasing body of research supports the notion that over time, diverging methylomes may account for substantial phenotypic discordance in monozygotic-twins and explain disparate susceptibilities to age-related disease. We review this evidence and discuss how a greater insight into the mechanisms of age-related epigenetic dysregulation may inform strategies for molecular diagnostics and therapeutic intervention.

Keywords: Methylome; Epigenome; Age-related disease; Epigenetic drift; CpG island; Methylome wide association study (MWAS); Monozygotic twins (MZ); Hutchinson-Gilford progeria syndrome (HGPS); Alzheimers disease (AD); Rheumatoid arthritus (RA); Type-2 diabetes (TD2); Stem cell exhaustion; Histone deacetylase (HDAC); Reactive oxygen species (ROS).

Introduction

The term epigenetics first arose to describe heritable changes in gene expression that did not involve changes to the base pair coding sequence of DNA, and to explain, in part, how cells with an identical genetic make-up can give rise to completely different tissue types [1]. A central effector involved in this process is DNA methylation, established by the covalent addition of a methyl group to cytosine residues in the context of cytosine-guanine di-nucleotides (so called "CpG sites") by DNA methyltransferase (DNMT) enzymes [2,3]. CpG sites are often not in isolation: rather, they are embedded in the genome as discrete clusters of CpG sites (termed CpG islands) that range in size from 0.5 to 2 kilobases and are frequently located in the 5' adjacent regions of transcriptional start sites [**3**]. With the advent of improved genome-wide methods to interrogate the methylome, discrete functional CpG sequences are continually being defined, for example CpG sites adjacent (within 2 kb) to CpG islands called "CpG islands shores", which are closely associated with somatically heritable, tissue-specific methylation patterns [4].

More than half of the genes in the genome contain CpG islands within their promoter and these islands are usually unmethylated in normal cells [3,5]. Methylation of CpG islands, however, can be detected at small subgroups of autosomal genes (<10%) in a tissue-specific manner. The functional role of CpG island [6] and CpG sites is context and loci specific and has been reviewed recently by Jones et al [7].

The establishment of the neonate methylome during embryogenesis is critical to development. Shortly after fertilization, the paternal and maternal genomes combine in the same cell and DNA methylation patterns are nearly completely erased [8-10]. Remarkably, select genes remain "imprinted" with methyl marks corresponding to the parent of origin and these imprinted genes are often maintained throughout the life of the offspring [10]. Genomic imprinting results in the restriction of gene expression to either the maternal or paternal allele [11].

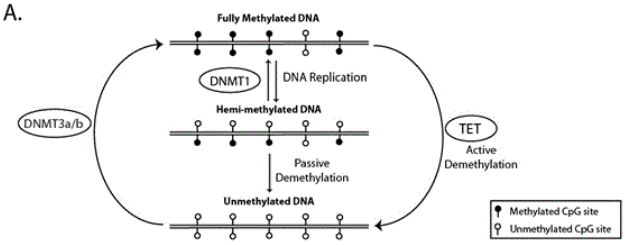

Figure 1: (A) Epigenetic maintenance of methylation at CpG dinucleotides. (A) Schematic illustration of the classical maintenance model for the propagation DNA methylation marks. After each round of replication, DNA is in a hemi-methylated state, with the daughter strand bearing nascent unmethylated CpG sites and the parent harboring the original CpG methylation status. Hemi-methylated DNA may undergo passive demethylation with another round of replication diluting out remaining methyl-CpG sites or hemi-methtylated DNA can be restored to its original methylation state through the activity of DNA methyltransferase 1 (DNMT1) maintenance enzymes. Ten-eleven translocation methylcytosine dioxygenases (TET) enzymes actively demethylate DNA.

Methylation marks are established throughout embryological development by de novo methyltransferases DNMT3a and DNMT3b [12]. Until recently, it was thought that as lineage specificity is established, DNMT3 enzymes were shut off and DNMT1 was expressed in order to maintain tissue specific methylation patterns in differentiated cells. However, there is increasing evidence that

DNMT3a is active in regulating gene expression in adult somatic cells, for example in mature neurons related to learning and memory [13,14]. The hypothesized first step in active cytosine demethylation is thought to be mediated by the recently discovered TET enzymes (ten-eleven translocation methylcytosine dioxygenases), which are able to catalyze the conversion of 5-methylcytosine (5mc) to 5-hydroxymethylcytosine (5hmc) [15,16]. Together, active methylation and demethylation events offer a model for the dynamic regulation of the genome (Figure 1A).

In combination with covalent modifications to histone (chromatin proteins) tails, somatic heritability of DNA methylation marks established during development leads to the persistence of highly tissue and cell type specific patterns of methylation [4,17-19]. For example, hypo methylation of the SRY (Sex-determining region on the Y chromosome) gene, encoding the master regulator of testis differentiation, results in transcriptional initiation of this gene exclusively in the gonads. In other tissue types, SRY is hyper methylated at the promoter region [20]. Additionally, differential methylation seems to be a critical mechanism involved in tissue reprogramming during the establishment of induced pluripotent stem cells (iPS) from somatic cells [21,22]. Because epigenetic events are dynamic and may be established in the absence of cell division, they can give rise to functional advantages that can be preferentially selected at much higher rates than somatic mutations and as such, are often early events in disease development [23,24]. There are a multitude of large-scale coordinated efforts to catalogue DNA cytosine methylation patterns and histone marks in the human epigenome [25], with additional efforts focused on the cancer epigenome [26].

In addition to DNA methylation marks, much of the functionality of the genome is dictated by the secondary structure of chromatin. At the smallest scale, the cell's genome is made up of two meters of helical DNA approximately 2 nm in width [27,28]. Helical DNA is further compacted by being wrapped in 1.65 superhelical turns around histone octamers forming a 10nm fibre, resembling "beads-on-a-string" [29,30]. Histone tails throughout the genome are subject to post-translational modifications, most commonly: acetylation, methylation, phosphorylation and ubiquitinylation. These modifications serve as binding sites for effector proteins, which read, write and erase histone marks and alter the degree of chromatin compaction accordingly [31]. In this way, the "histone code"—defined by combinations of distinct histone tail modifications—regulates dynamic transitions between transcriptionally active and silent chromatin states [32].

Aging is characterized by a gradual loss of tissue function, physiological integrity, reduced fidelity of cellular processes and functions, such as DNA repair, and ultimately an increased susceptibility to cell death. Disruptions of epigenetic processes are risk factors in several age- related human pathologies such as Hutchinson-Gilford Progeria Syndrome (HGPS), Alzheimer's disease (AD), Rheumatoid Arthritis (RA), Type-2 diabetes (TD2) and cancer. Aging research has experienced an explosive growth over recent years and many of the hallmarks of aging are now being elucidated (reviewed in [33]); however, a greater understanding of the epigenetic pathways contributing to age-related disease and the control of the rate of aging is needed. Here, we review the current state of knowledge of how the epigenome changes with age, and therefore may be involved in age-related diseases, and we further summarize plausible mechanisms mediating methylation drift.

Epigenetic Changes in the Aging Cell

At the whole genome level, aging is associated with a global loss of DNA methylation [34-36] and a concurrent, site-specific, increase in DNA methylation [37-40]. The positive correlation between increased methylation of CpG islands and shores with age was confirmed by a recent MWAS (methylome-wide association study) conducted on blood DNA from 718 men and women ranging in age from 25–72 [41]. In this study age-related methylation changes mapped to multiple genes, including: protocadherin genes (implicated in neural circuit development), homeobox genes (associated with aging and cellular senescence), ryanodine receptor genes (linked with aging and senescence) and mitogen-activated protein kinase genes (involved in regulating senescence) [41]. To define intra-individual methylation changes associated with aging, a longitudinal study compared global DNA methylation patterns of blood sampled from the 126 subjects, 16 years apart and found time-dependant marks of aging, including among others, Absent In Melanoma (AIM2) and Colony-Stimulating Factor 3 Receptor (CSF3R) [42]. Interestingly, AIM2 is an immunological mediator promoting the release of pro- inflammatory cytokines in senescent cells that contribute to age-associated inflammatory diseases [43,44].

Changes to the epigenome are thought to contribute to the physiological, and even behavioural, changes that arise through the process of aging [45]. A classic system in which to study the role of non-genetic factors in aging are monozygotic twins (MZ). A study by Manel Esteller's group showed that MZ twins, though they share virtually identical DNA sequences, display significant epigenetic differences that could account for phenotypic discordance between them [46]. The epigenomes of young MZ twins are very similar but patterns of methylation in MZ pairs diverge as they age. Epigenetics represents the crucial link between the genome and the environment; thus, epigenetically distinct landscapes in older twins can be explained, in part, by exposure to different environmental factors. Lifestyle choices, such as smoking habits, physical activity and diet, all contribute to the formation of age-accumulated epigenetic layers that modulate patterns of gene expression [46]. Further, it was shown that MZ twins who had spent more time apart had significantly different epigenomes and concomitant gene expression profiles than MZ twins who had lived together and shared a similar environment [46,47]. Indeed, epigenomic analysis of a rare pair of MZ twins discordant for Alzheimer's disease (AD) revealed substantial differences in DNA methylation in the temporal neocortex [48].

Clearly the phenotype of an organism is dependent upon both genetic and environmental variance; however, there is a noteworthy third factor that contributes to phenotypic discordance and that is biological stochasticity. A study performed in clonal crayfish found that there was significant developmental variability of the crayfish, at all life stages, despite having identical genomes and being raised in the same environment [49]. Therefore, contributions to epigenetic and phenotypic variability may also arise from a combination of genetic, environmental, and ill- defined "stochastic" factors [37].

Another epigenetic layer of the histone code is also known to have a distinctive profile in aging and in cancer. Generally, open or euchromatic chromatin structures are associated with acetylation of histone tail residues and de-acetylation of these residues are associated with closed or heterochromatic chromatin states; however, the establishment of a combinatorial pattern of multiple types of histone post-translational modifications ultimately directs chromatin compaction and guides gene expression. It has been well documented

that modulation of the histone code has profound effects on a multitude of nuclear processes, such as DNA damage repair, heterochromatin maintenance, gene expression and telomere attrition, which are linked with aging. For example, the histone mark H4K20me3 (i.e., tri methylation of the lysine (K) that is the 20th amino acid on histone 4) is prevalent in differentiated tissues [50] and is known to increase with age [51]. Further, independent studies corroborate that methylation of H4K20 increases progressively with age in murine models and the abundance of this mark is positively associated with senescence [38,51]. While histone modification maps are likely relevant to aging phenotypes, exactly how changes in patterns of histone modifications contribute to the pathophysiology of aging remains to be elucidated.

Epigenetic defects acquired throughout life are believed to affect the behaviour of adult tissue-specific stem cells [52]. The declining function of these somatic stem cells, a process known as stem cell exhaustion, contributes to reduction in repair capacity, tissue homeostasis and loss of physiological integrity [33]. This attrition of stem cell activity can arise due to age-related accrual of genetic lesions (reviewed in [53]) and epigenetic alterations (reviewed in [52]). Studies in murine models show that nascent haematopoietic stem cells (HSCs) undergo asymmetric cell division more frequently than aged HSCs [54]. Although the number of stem cells does not necessarily decrease with age, their functional regenerative capacity (ability to make more progenitors) diminishes, leading to a loss of proliferative potential and tissue reconstitution [54]. Thus, older individuals, whose stem cells have undergone successive rounds of DNA replication and have been subjected to a greater degree of genetic and epigenetic instability, are more prone to stem cell exhaustion, loss of tissue homeostasis (one of the hallmarks of aging) and development of age-related disease, such as cancer [53,55]. Some have hypothesized that the secrets of youthfulness and age are inextricably linked to the epigenetic states of adult stem cells and their capacity for quiescence and self-renewal (reviewed in [56]).

Epigenetic Changes in Age-related Diseases

Since epigenetic systems normally modulate profound expression and phenotypic changes throughout a cell's life, it follows that dysregulation of epigenetic patterns, as observed with aging, may contribute to age-related disease. The information contained in the epigenetic state of DNA and chromatin influences the expression of well-documented oncogenes, such as cMYC, TERT (regulators of proliferation and replicative immortality), and tumour suppressor genes, such as P53 and RB1 (regulators of senescence, among other features) [57]. Abnormal expression patterns of oncogenes and tumour suppressor genes have profound effects on the initiation and development of many cancer types [58]. Interestingly, many of the epigenetic alterations and chromatin changes that are hallmarks of aging [33], are also closely linked to cancer susceptibility and tumorigenesis [58-60]. For example, in cancer, DNA hypomethylation occurs globally frequently at repetitive DNA elements, which is thought to contribute to increased chromosomal instability [61,62] and the activation of transposons [63] (Figure 1B). Further, in malignant cells, tumor-type-specific transcriptional silencing of tumour suppressor genes (TSGs) is strongly correlated with hypermethylation of their associated promoters [64-76]. The same trend—widespread DNA hypomethylation and focal CpG island hypermethylation—is also observed in epigenome of human senescent cells [57]. Hypomethylation of interspersed repetitive sequences, such as Long Interspersed Elements (LINEs), Short Interspersed Elements (SINEs) and LTR retrotransposons, occurs progressively with age and is linked to a decline in organ function [77-81]. Additionally, an age-dependant hypermethylation signature can be seen in the promoter regions of genes normally targeted by Polycomb Group (PcG) proteins, which are proteins involved in transcriptional silencing [82]. Interestingly, this age-PcG target methylation profile can be used to distinguish normal cells from pre-invasive cancer cells [82]. Methylation changes associated with aging have also been observed in the transformation of a normal cell into a cancer cell (reviewed in [35]), thus some have suggested these changes may contribute to the increased risk for cancer with age [59].

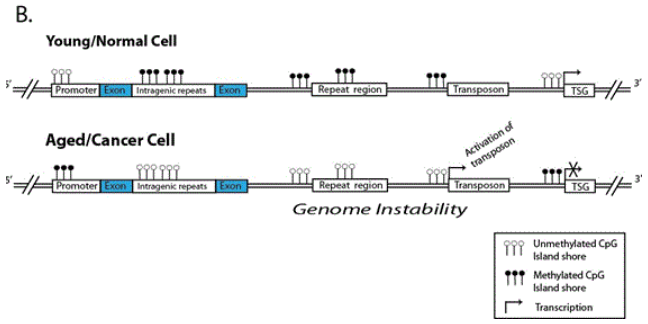

Figure 1: (B) Pattern of DNA methylation marks during aging and cancer. CpG sites in the promoter regions of genes undergo focal hyper methylation in aging and cancer; while, intra and extragenic repeat regions as well as transposable elements show an increased propensity for demethylation, leading to genomic instability. TSG: Tumour Suppressor Gene.

One disease that might reveal clues about the physiological mechanisms of aging is Hutchinson-Gilford Progeria Syndrome (HGPS)—a rare disorder causing affected individuals to age at ten times the normal rate [83]. Patients with HGPS usually manifest symptoms of aging, such as limited growth, hair loss, wrinkled skin and lipodystrophy, at a very early age [83-86], and typically die from cardiovascular disease or atherosclerosis at around 13 years of age [83]. Progeria is caused by a mutation in the LMNA gene, encoding for nuclear lamina, which is present on the inner side of the nuclear membrane (reviewed in [87]). Nuclear lamin are fibrous proteins which form a highly dynamic meshwork between the inner nuclear membrane and chromatin [88]. Mutations or aberrant splicing of lamin-A results in the accumulation of a dominant negative form of lamin-A, called progerin, that becomes constitutively farnesylated and anchored in the nuclear membrane [86]. Progerin accumulates gradually as a physiological consequence of normal aging; however, in HGPS patients, progerin agglomerates at an accelerated rate. Increased levels of nuclear progerin have been linked to many age-related phenotypes including: telomeric aberrations, defective DNA repair, mitochondrial dysfunction, altered cell cycle regulation and cellular senescence [86,89,90]. Interestingly, the epigenetic architecture of HGPS mimics the epigenetics of normal aging [86].

Nuclear lamins play a crucial role in higher order chromatin organization and the regulation of gene expression (reviewed in [91]). Recently, it has been shown that epigenetic modifications known to regulate the dynamics of chromatin organization might be involved in the underlying physiology of HGPS [86,92,93]. In HGPS cells, the

non-random arrangement of chromosomes into discrete territories is perturbed due to the presence of abundant progerin. The consequences of such distortion are a loss of peripheral heterochromatin, rampant nuclear disorganization and nuclear lobulation or blebbing [89,94]. Of note, several proteins involved in maintaining nuclear architecture, such as barrier-to-autointegration factor (BAF) [95], inhibitor of growth protein 1 (ING1) [96] and D4Z4 [97], are also frequently lost in progeroid cells. In addition to aberrations in nuclear architecture, HGPS patients display a substantial down regulation of the histone variant γH2AX, an important marker of DNA repair. This down regulation of γH2AX likely contributes to the accumulation and persistence of DNA damage in HGPS cells [98]. As is the case with cellular senescence, fibroblasts from individuals with HGPS display a loss of two histone marks associated inactive chromatin, H3K27me3 and H3K9me3 [93,99,100]. In support of these findings, it has been shown that pericentric regions (genomic regions normally embedded in silent chromatin) are transcriptionally active in HGPS cells that lose H3K27me3 [99]. In addition to loss of H3K27me3 and H3K9me3, loss of H4K16 acetylation, a mark important in the DNA damage response, has also been reported in an animal model of this disease [101]. Interestingly, treatment of mice with sodium butyrate, a compound that inhibits histone deacetylase enzymes, revived levels of H4K16 acetylation and rescued mice from the progeroid phenotype [101].

Other non-oncogenic diseases, such as Alzheimer's disease (AD), are strongly associated with aging and can also be linked to specific epigenetic alterations [102,103]. AD is a progressive neurodegenerative disorder that can occur in old age and is often characterized by accumulation of amyloid β peptides and abnormally phosphorylated tau proteins [104,105]. The altered methylation state of the AD brain typically results in gene expression alterations in two primary pathogenic pathways: amyloid precursor protein (APP) processing and tau hyper phosphorylation [102,106]. For example, one study found that glioblastoma cells which express 2.6-fold higher levels of APP display a global reduction DNA methylation and this hypomethylation resulted in the ectopic expression of several AD-associated genes such as PS1, BACE1 and APP itself [107]. In the rat model of AD, increased H3 acetylation and decreased promoter methylation in the region of cyclin dependant kinase 5 (cdk5), lead to increased hippocampal cdk5 activity, tau phosphorylation, synaptic dysfunction and memory loss [104].

It has been shown that DNA methylation in the forebrain, which is maintained by Dnmt1 and Dnmt3a, is intricately involved in regulating synaptic function and memory formation [108-110] Indeed, both aging and cognitive impairment are associated with global DNA hypomethylation and widespread down regulation of Dnmt1 and Dnmt3a in the hippocampus [111,112]. This finding is exacerbated in individuals with AD [113-115]. Thus, aging-associated defects in hippocampal DNA methylation might underlie the spatial memory deficits characteristic of AD. Interestingly, a genome-wide brain DNA methylation study found that many differentially methylated genes identified in late-stage AD brains also occurred in presymptomatic AD brains, raising the possibility that these DNA methylation alterations may be an early feature of AD pathology. Early DNA methylation alterations at ankyrin 1 (ANK1), disco-interacting protein 2 (DIP2A), rhomboid family member 2 (RHBDF2), ribosomal protein L13 (RPL13), SERPINF1 and SERPINF2 are connected to a network of known AD susceptibility genes and may have a role in the onset of AD [116]. In another study, two genes, SORBS3, involved in cell adhesion, and S100A2, a calcium binding protein, have been found to become progressively more methylated with age and their methylation becomes accelerated in patients with AD [95]. However, not all genes implicated in AD pathogenesis are associated with age-related changes in DNA methylation. One gene involved in β-amyloid post-translational processing, TMEM59, is hypermethylated in AD patients but remains relatively unaffected in elderly controls [117]. Additionally, in other age-related diseases, such as rheumatoid arthritis (RA) and type 2 diabetes (TD2), methylation changes have been implicated–an MWAS identified characteristic methylome signatures in RA [118,119] and work by Ronn et al. showed that age-related promoter hypermethylation of COX7A1, a gene important for glucose metabolism, might contribute to the onset of TD2 [120].

Mechanism of Age-related Methylation Drift

Since epigenetics is the interface between environmental agents and genomic programming, it follows that the accumulation of environmental damage correlates with epigenetic dysregulation and with the pathogenesis of age-related disease [121]. One mechanism of epigenetic dysregulation occurs through methylation drift— the stochastic change in DNA methylation patterns at certain loci, reflective of the imperfect maintenance of epigenetic machinery [55,66]. Considering the accuracy of DNA methyltransferase enzymes (95% for DNMT1), methylation patterns is bound to become inaccurate with numerous passages through the cell cycle (Figure 2A) [122-124].

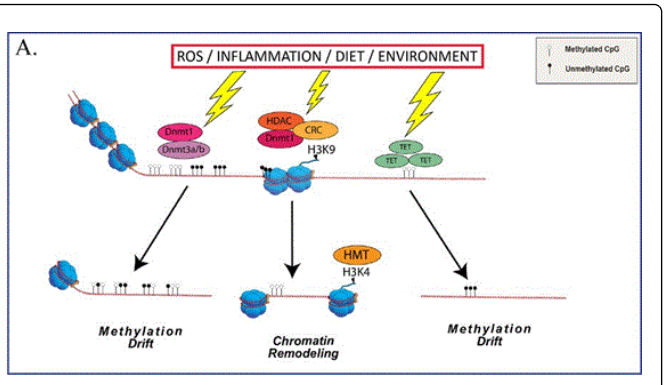

Figure 2: (A) Mechanisms of epigenetic drift. External/endogenous factors such as ROS, inflammation, diet and other environmental stresses can cause lesions in epigenetic maintenance systems. Loss of fidelity of methylation transferase enzymes (left) or demethylation enzymes (right) leads to aberrant propagation of CpG methyl marks and methylation drift. Disruption of enzymes that modify the histone code (middle) can result in a rearranged chromatin secondary structure and subsequent aberrant CpG methylation. ROS: Reactive Oxygen Species; Dnmt1: DNA methyltransferase 1; Dnmt 3a/b: DNA methyltransferase 3a/b; HDAC: Histone Deacetylase; CRC: Chromatin Remodeling Complex; TET: Ten-Eleven Translocation Methylcytosine Dioxygenases; HMT: Histone Methyltransferase.

Stochastic differential methylation patterns that arise in aging individuals create an epigenetic mosaicism that may allow for the selection of biological defects leading to cancer and other age-related diseases (Figure 2B) [2,55,66,125]. Generally, methylation drift (differential site specific hypo- or hypermethylation) occurs in all individuals past a certain age [41]; however, rates of methylation drift

vary depending on local transcriptional activity [126], the methylation state [127], histone tail modifications [128-130], polymorphisms in gene sequence [131-133] and activity of trans-acting factors such as DNMTs, TETs [134], DNMT3L [135], CTCFs [136] and long-noncoding RNAs [137].

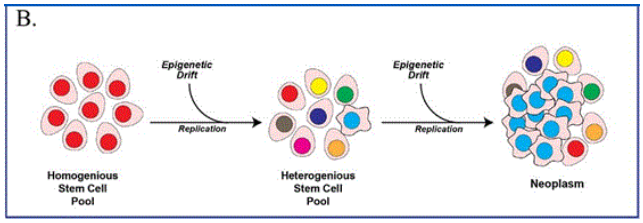

Figure 2: (B) Epigenetic changes may initiate cancer phenotypes by priming cells in such a way as to make them more susceptible to subsequent pathological genetic or epigenetic changes. Young stem cell populations, after successive rounds of replication and greater accrual of epigenetic drift, become a mosaic population of stem cells with epigenetically different landscapes. Continued replication and epigenetic drift leads to stem cell exhaustion and/or selection of cells with a proliferative advantage.

In addition to the dysregulation of enzymes that write the DNA methylome, a critical regulatory mechanism of methylation drift lies in the fidelity of enzymes that erase the methylome (Figure 2A). As previously mentioned, the recently discovered TET family of dioxygenases is believed to mediate the oxidation of 5mC thereby priming it for removal by the Base Excision Repair pathways (BER) [92]. Disruption of the epigenetic machinery responsible for active demethylation can lead to age-specific 5hmC profiles [138] and/or DNA demethylation profiles [139]. Interestingly, methylation drift is associated with promoter hypomethylation of PSEN1 and APOE-genes important in the age-dependant onset of neurodegenerative diseases such as AD [139]. A major source of sequence mutations in the human genome is spontaneous deamination of methylated cytosines which occurs when methylated cytosines undergo hydrolysis and subsequent conversion into thymine, resulting in a T:G base pair mismatch [140]. This mismatch, leads to the general depletion of CpG dinucleotides from mammalian genomes [141] and the accumulation of sequence mutations which may be deleterious over time [142].

Chemical modifications to DNA are not isolated events, but occur as part of a complex chromatin network that is mediated by extensive cross talk between different post-translationally modified histone structures and proteins, thus disruption of any one of these components can lead to deleterious epigenomic effects [3,73,143-145]. One enzyme which modifies the histone code to regulate specific biological process is Sirtuin1 (SIRT1)—an NAD+-dependant, class III Histone Deacetylase (HDAC) that plays a role in senescence, aging and cancer development [146,147]. HDACs, such [120] as Sirtuins, can regulate gene expression by removing acetyl groups from lysine residues on histone tails causing chromatin to re-order into a more condensed transcriptionally inactive state [148]. Early studies of the sirtuin homologue, silent information regulator 2 (SIR2), in multiple organisms have shown that SIR2 can the increase life span [149-151]. Over the past years, studies in mammals have shown that SIRT1 is expressed in most tissues and its expression is reduced in senescent cells [152] and during aging [153]. Caloric restriction [154], cellular stress [155-157] and polyphenols (such as resveratrol) [147] stimulate the activity of Sirt1, which leads to cell survival and longevity by increasing transcriptional silencing and genome stability, fat metabolim and stress resistance [158]. The oncogenic potential of Sirtuins stems from their role in controlling several central molecular pathways, many of which are directly involved in cancer. For example, Sirt1 directly deacetylates and inactivates TSGs such as p53 [159], HIC1 [160] and p73 [161], and is implicated in the dysregulation of energy homeostasis, the hypoxic response, the PI3K/AKT signaling pathway, TGF-β signaling, Wnt signaling and DNA damage repair (reviewed in [162]. At the chromatin level, upregulation of Sirt1 during tumorigenesis could lead to the establishment of a cancer-specific histone modification profile [144,163,164]. Consistent with the observation that Sirtuin proteins are tightly linked to cellular metabolic pathways [165], upregulation of Sirt1 in mice has been shown to ameliorate symptoms of a variety of age-related metabolic diseases including TD2, AD and cancer [166].

Epigenetic Based Diagnostic and Therapeutic Strategies

DNA methylation profiles are relatively malleable and are often early neoplastic events, thus the exploration of epigenetic marks as early detection, diagnostic and predictive biomarkers is an enormous field of study (reviewed in [60]). Moreover, in contrast to DNA sequence level alterations, epigenetic modifications are reversible. Epigenetic based drugs which reverse aberrant DNA methylation or histone profiles (albeit non-specifically) through the inhibition of DNMT or histone modifying enzymes (specifically histone deactylase inhibitors, HDACs) are approved chemotherapies for some malignancies. The assessment and development of epigenetic-based treatment strategies for a broad variety of cancer types is an active field of cancer research [167]. Since the epigenome can also be modulated by diet, prevention is an emerging field of research for malignant and non-malignant disease. For example, epigenetic modifications implicated in the pathogenesis of Alzheimer's disease, such as genes involved in neural pathways for learning and memory are found to be hypomethylated in AD [168]; therefore, it is postulated that dietary supplementation with methyl donors (i.e. folate) may help restore cognitive performance that declines with age [169,170]. HDAC inhibitors have also been shown to have potential clinical relevance in AD; valproic acid, a pan-HDAC inhibitor, was shown to lead to a reduction in β-amyloid production and alleviate behavioural deficits in murine models of AD [171]. Currently, epigenetic-based drugs are non-specific; however, as knowledge about the mechanisms guiding specificity of epigenetic machinery emerges, the targeting of epigenetic based therapeutics will no doubt improve. Encouragingly, since an individual's epigenome can be modulated by healthy dietary and lifestyle choices (e.g., increased intake of vegetables, quitting/not smoking); reduced risk of disease associated with these healthy choices may be in part modulated epigenetically.

Conclusion

It is clear that the biological pathways underlying age-related disease are associated with epigenetic dysregulation, however many questions remain unanswered regarding i) the precise mechanisms governing these processes, ii) timing and iii) interactions between an individual's environment, epigenome and genome. With the advent of powerful new experimental pipelines built around high-throughput next generation sequencing, initiatives such as The Encyclopedia of DNA Elements (ENCODE) consortium [172,173] and The NIH

Roadmap Epigenomic Mapping Consortium, have undertaken large-scale coordinated efforts to catalogue DNA cytosine methylation patterns and histone marks in the human epigenome. In conclusion, a greater understanding of the epigenetic basis of age-associated disorders is needed to inform the development of exciting new therapeutic intervention and prevention strategies targeting these diseases. As the population of elderly individuals continue to grow, these questions become increasingly pertinent.

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