Review Article

Age-Related Epigenetic Dysregulation in Cancer Development: From Mechanisms to Therapeutic Targets

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ABSTRACT

In 2021, it was estimated that one in ten people were over 65. This proportion of elderly people is only expected to increase, with projections expecting one in six people to be over 65 by 2050. Consequently, as the aging population, particularly in regions like the United States, continues to grow, understanding how the process of biological aging increases susceptibility to the development of cancer is becoming increasingly important. Indeed, understanding the epigenetic changes that occur with biological aging is becoming vital for addressing the increasing prevalence of age-related diseases, especially cancer. This paper will explore the connection between epigenetic processes and aging, underlining how this affects the deterioration of epigenetic regulatory systems overall. Furthermore, this paper will subsequently explain how the deterioration of key epigenetic mechanisms, such as DNA methylation and histone acetylation processes, leads to age-related diseases, with a specific focus on cancer. Approaching age-related diseases from an epigenetic perspective offers a valuable viewpoint for medical interventions. In fact, this approach to medication is presenting a promising way forward for our increasing aging population, as evidenced by Histone Deacetylase Inhibitors (HDACis) and DNA Methyltransferase Inhibitors (DNMTis) showing anti-tumor effects in clinical trials.

Keywords: Biology; Epigenetics; Cancer; Aging; Age-related diseases; DNA; Histones

INTRODUCTION

Aging is characterized by a decline in bodily function and increased susceptibility to age-related diseases such as cancer, cardiovascular diseases, neurodegenerative disorders, and metabolic disorders (21). Outward signs of aging also include gray hair, wrinkles, and age spots on the skin (22). Statistically, in 2021, it was estimated that one in ten people were over 65, and this proportion of elderly people is only expected to increase, with projections expecting one in six people to be over 65 by 2050 (28). Therefore, addressing the issue of an aging population has become paramount due to its implications for individuals, societies, and healthcare systems. For instance, an aging population may lead to increased healthcare costs and resource allocation, as well as having an economic impact on countries. Moreover, this can also have numerous social impacts, such as increased dependency on family

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members in the working population and isolation among elderly people (29). Given these challenges, one promising way to address the issue of aging is from the epigenetics perspective, specifically by confronting the epigenetic factors implicated in many age-related diseases. Consequently, designing drugs that will address specific epigenetic aspects contributing to greater susceptibility to cancer holds great potential.

OVERVIEW OF AGING THEORIES AND THE RISE OF EPIGENETICS

There are many different plausible theories explaining why people age biologically, which have been reviewed in depth by Maynard et al. (2015) and Chilton et al. (2017) (5, 13, 26, 8). The most prominent of these theories include:

- The evolutionary theories of aging: One such theory states that a reason people age biologically could be due to natural selection. This theory posits that the force of natural selection grows weaker as one ages, shifting priorities from enhancing survival and reproduction to allowing the accumulation of deleterious mutations.
- Cellular senescence theory of aging: Another example is the theory of aging focusing on mechanisms affecting homeostasis, such as cellular senescence.
- Disposable soma theory of aging: Additionally, the disposable soma theory suggests that humans evolved such that greater metabolic resources are allocated to growth and reproduction instead of repairing stochastic damage. Thus, after necessary growth and reproduction, repairing stochastic damage—for example, DNA damage caused by ionizing radiation—gradually becomes less of a priority.
- DNA damage and repair theory of aging: The DNA damage and repair theory of aging—which falls under a broader category of theories where the main cause is the decline in molecular fidelity—proposes that aging is caused by the continual decline of biomolecular fidelity after reproduction, as time after this is deemed biologically superfluous.
- Mitochondrial and free radical theory of aging: Lastly, the mitochondrial and free radical theory of aging states that mitochondrial damage, including the accumulation of mitochondrial DNA mutations and the release of reactive oxygen species (which is linked to nuclear genomic instability), leads to physiological aging (18).

While many of these theories are plausible and may explain why people age biologically, some theories, such as the mutation theory of aging which involves the accumulation of DNA mutations causing aging, have been called into question. In this case, the theory was challenged because aged cells often had few mutations, and conversely, cells with many mutations did not always show signs of aging (23). Because of these limitations and emerging evidence, scientists have increasingly turned to the epigenetic theory of aging. Epigenetics is the study of how DNA is organized and expressed and how that subsequently affects organisms (20). Notably, epigenetic aging, often tracked by the progression of the DNA methylation clock, has been associated with common diseases such as diabetes, osteoporosis, sarcopenia, and cancer. Subsequently, changes in the epigenome have increasingly become a topic of focus for papers researching cancer development. In this paper, I will therefore mainly discuss the epigenetics of an age-related disease, specifically cancer, due to its prevalence and significant impact on health.

EPIGENETIC MECHANISMS IN AGING

Chromatin, the complex of DNA and proteins within the nucleus, is made up of repeating units of nucleosomes. The nucleosome itself consists of core histone proteins forming an octamer, around which DNA strands are wrapped. Epigenetic mechanisms involve chemical modifications of the nucleosome, affecting chromatin structure and, in turn, regulating gene expression. Common epigenetic changes in chromatin include methylation, histone acetylation, and phosphorylation. Critically, in epigenetics, while the DNA sequence is not altered, these epigenetic modifications can cause genes to be expressed in different ways. These changes involve chemically modifying structures that control the expression of DNA and proteins associated with DNA (6). One such example of how epigenetic changes cause genes to be silenced or amplified is seen in the distinct states of euchromatin and heterochromatin. The differences between these two lie in their transcriptional accessibility and compactness. Euchromatin is the less compact, more transcriptionally accessible form of DNA, allowing greater expression of genes. On the other hand, heterochromatin is the more compact, less transcriptionally accessible form, thereby suppressing the expression of genes (8). For instance, euchromatin is typically associated with the methylation of the amino acid residue lysine 4 on the histone H3 protein (25), and it is additionally associated with the acetylation of histones H3 and H4 (8). Conversely, heterochromatin is associated with the hypoacetylation of histones (8).

The aforementioned DNA methylation, histone acetylation, and phosphorylation processes are key modifications affecting gene expression. For example, normal DNA methylation suppresses genes appropriately, but hypermethylation can silence necessary genes, while hypomethylation may activate harmful ones. Similarly, histone acetylation generally loosens chromatin for transcription; however, misregulation of this process disrupts gene expression, contributing to diseases. Phosphorylation also alters chromatin structure to regulate transcriptional activity, with imbalances potentially either enhancing or suppressing gene expression, leading to aging and related disorders.

A recent theory proposed by Steve Horvath, known as Horvath's clock, suggests that specific DNA methylation patterns can determine biological age. This theory posits that aging is primarily caused by cumulative epigenetic changes as opposed to a loss of DNA information, building on growing evidence that aging is significantly influenced by epigenetic factors. Using this as a basis, biological age is determined specifically as an accumulation of changes in these epigenetic patterns (14). While it had previously been believed that as one aged, the DNA "code" was lost, it has now been found that aging may actually occur because of epigenetic changes—that is, changes in how DNA is organized and read. Sinclair et al. (referring to work like Lu et al., 2020) postulate that this kind of epigenetic information loss causes aging (19, 23). This is because, over time, histones, which are proteins that act as spools for DNA, may not return precisely to their original state after they are involved in gene regulation. Furthermore, the DNA methylation process can also be error-prone, sometimes adding methyl groups in the wrong place. Thus, when methyl groups are incorrectly placed in the promoter of a certain gene, it can repress gene transcription and thereby prevent the gene from being expressed (23).

DNA and Histone Modifications

Such epigenetic changes that can affect one's susceptibility to age-related diseases include abnormal histone modifications and DNA methylation. This abnormal modification can change gene expression, promoting aging-associated changes in the transcriptome. The N-terminal tails protruding from the four main histones can undergo various post-translational modifications—including phosphorylation, ubiquitination, histone acetylation, DNA methylation, and proteolysis—which ultimately determine the structure of chromatin, categorizing it as either euchromatin or heterochromatin. All of these post-translational modifications alter the transcriptional accessibility of chromatin, thereby influencing pathogenesis. DNA modifications refer to chemical changes to the DNA molecule itself, primarily DNA methylation. Histone modifications involve the addition of small chemical groups to histone proteins.

DNA and Histone Methylation

Regarding DNA modification specifically, DNA methylation generally results in the suppressed transcription of genes when methyl groups are added to their promoter regions. DNA methylation typically involves a methyl group being added to a promoter such that the transcription of the associated genes is restricted. When methyl groups are added to cytosine bases, the proteins that normally control the transcription rate may become unable to bind effectively with the gene promoter. In other words, this can effectively block other transcription factors and proteins responsible for transcription from successfully binding, thus inhibiting gene transcription (2). Histone methylation, on the other hand, involves adding methyl groups to histone proteins themselves, which alters chromatin structure and gene expression. Specifically, this modification often makes the chromatin structure more compact, thereby suppressing gene expression (Figure 1).

DNA and Histone Acetylation

Additionally, histone acetylation generally results in greater transcriptional activity. Histone acetylation effectively neutralizes lysine's positive charge and commonly occurs on the N-terminal tails of nucleosomal histones. The neutralization of lysine's positive charge allows the chromatin to decondense, thereby allowing greater access for transcriptional mechanisms within the chromatin (10). Histone acetylation similarly adds acetyl groups to histone proteins, typically creating a more open chromatin structure and resulting in greater gene expression (Figure 2).

Several studies have suggested that there are potential epigenetic-related therapies to treat age-related diseases precisely because of the influence of these epigenetic factors (15). For instance, a study conducted on mice further supports the argument of the epigenetic information theory of aging. The purpose of this study was to determine whether the aging process led to genetic information being irretrievably lost or whether that information was still present and could potentially be restored. The study aimed to elucidate whether the information could be restored, allowing the aged cell to

regain its function. This particular study reprogrammed epigenetic information to restore youthful epigenetic patterns and vision in the mice (19).

Using an eye cell as a model of the central nervous system, the study showed that expression of the Yamanaka factors Pou5f1 (Oct4), Sox2, and Klf4 (OSK) in the retinal ganglion cells of aged mice was able to reverse signs of aging in these cells, restore vision, and reimpose youthful DNA methylation patterns. Therefore, the reversal of the DNA methylation clock and restoration of youthful function in these mice demonstrates that youthful epigenetic information is not permanently lost, and the appropriate re-expression of this epigenetic information can reverse the adverse effects seen in aged cells (19).

Furthermore, another study highlighted how transient epigenetic reprogramming, related to the epigenetics of aging, can promote rejuvenation in human cells. The study found that transient expression of OSKM factors (OCT4, SOX2, KLF4, and MYC)—proteins used to reprogram cells—causes key epigenetic modifications. It was found that these changes correlated with the reversal of aging-related gene expression. The study also indicated that these changes reversed biological age, as measured by the DNA methylation clock, and reversed physiological markers of aging in cultured human cells (10, 19 and related works like Ocampo et al., 2016).

Overall, this body of research signifies that there is a large epigenetic component to the aging of cells and organs in the body. These epigenetic changes can cause cells to age due to certain important genes being turned off or because of the inappropriate encouragement of genes that contribute to disease. For example, the DNA methylation of promoters of tumor suppressor genes could enhance the progression of cancer, while the histone acetylation of such genes might, in some contexts, resist the progression of cancer. The progressive weakening of epigenetic systems through misregulation of certain genes causes variations in histone modifications and DNA methylation patterns. Furthermore, key variations in these epigenetic marks have been associated with older ages, contributing to the development of age-related diseases such as cancer, osteoporosis, cardiovascular diseases (like coronary heart disease), and several neurodegenerative diseases (such as Alzheimer's disease and dementia).

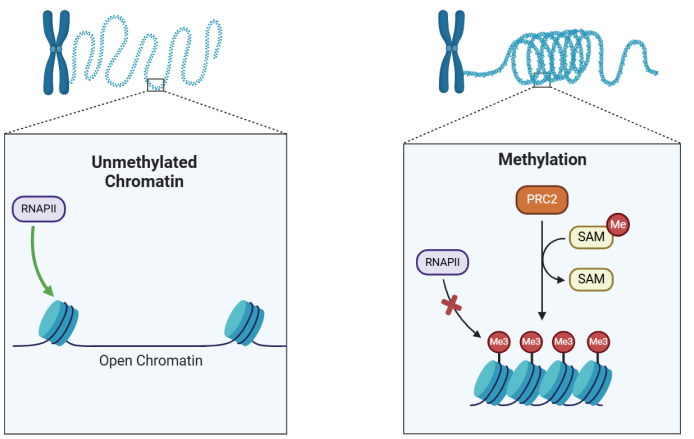

Figure 1. Mechanism of Methylation by PRC2 and Its Impact on Transcription. Polycom Repressive Complex 2 (PRC2) facilitates addition of methyl groups to chromatin. The left panel depicts unmethylated chromatin, which has an open structure conducive to transcription. As shown in the right panel, in the presence of S-adenosylmethionine (SAM), PRC2 transfers methyl groups (Me) onto specific lysine residues on histones, resulting in methylated chromatin. This modification leads to a closed chromatin conformation, effectively blocking RNA Polymerase II (RNAPII) from accessing the DNA and blocking transcription. Overall, this highlights the repressive effect of methylation from the left to right on gene expression.

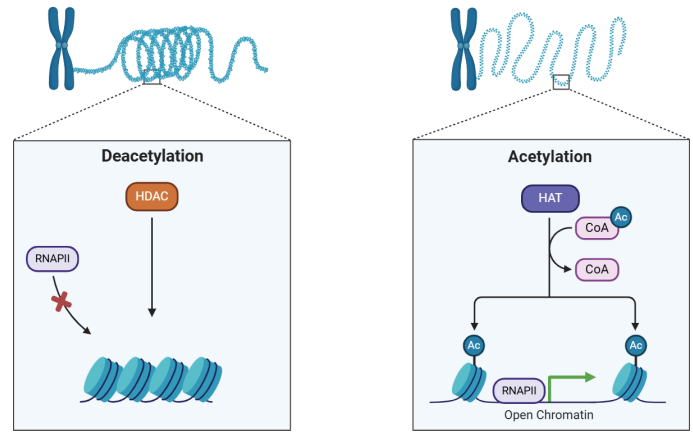

Figure 2. Mechanisms of Acetylation by HAT and Its Impact on Transcription. Histone Acetyltransferases (HAT) facilitate addition acetyl groups to chromatin. The left panel depicts deacetylated chromatin, which has a closed structure that is not conducive to transcription. As shown in the right panel, in the presence of Acetyl Coenzyme A (CoA), HAT transfers acetyl groups (Ac) onto specific lysine residues on histones, resulting in acetylated chromatin. This modification leads to an open chromatin conformation, effectively allowing RNA Polymerase II (RNAPII) to access the DNA, enabling transcription. Overall, this highlights the activating effect of acetylation from the left to right on gene expression.

Consequently, chronological age, and particularly biological age as reflected by epigenetic markers, is associated with these diseases because of the epigenetic changes that may gradually occur as one's chronological age increases. Epigenetic changes that affect one's susceptibility to age-related diseases generally include histone variant accumulation, deregulated expression of microRNAs, and abnormal histone modifications and DNA methylation.

THE EPIGENETICS BEHIND CANCER

Cancer risk generally increases as one ages, partly as cell mechanisms start to deteriorate. One of the reasons for the deterioration of cells is indeed due to epigenetic factors (4). Cancer can develop when damage is incurred by a cell's DNA in a way that causes the cell to proliferate uncontrollably. Yet, there are different intrinsic mechanisms that resist tumorigenesis, such as cellular senescence. Cellular senescence is the irreversible exit of a cell from the cell cycle, and it can be caused by epigenetic shifts, external stresses (e.g., sun exposure, chemicals), and metabolic stresses (natural stresses within the cell). Essentially, cells that become "senescent" stop dividing, which can halt the initial development of cancer. However, over time, senescent cells can eventually release chemicals that cause inflammation. Specifically, senescent cells release proinflammatory factors as part of the senescence-associated secretory phenotype (SASP). This SASP can disrupt immune system functionality, including causing impairments in T-cell activity, thereby potentially exacerbating age-related diseases (7).

The deregulation of histone modifications can significantly impact cell function by disrupting normal cellular homeostasis. Such histone modifications include methylation, histone acetylation, and phosphorylation. For example, misregulation of these marks can activate oncogenes or could suppress tumor suppressors. Moreover, there is an intricate interplay between histone modifications and DNA methylation, where changes in one epigenetic mechanism often correlate with, or influence, changes in the other (16, 9).

Role of DNA Methylation in Cancer Development

MLH1 (MutL Homolog 1) is a gene that plays a critical role in the DNA mismatch repair (MMR) pathway. It is frequently silenced in sporadic cancers. The result of MLH1 silencing is a decrease in DNA MMR activity, leading to increased genetic instability and a "mutator phenotype," where a cell's mutation rate dramatically increases—a common feature in cancer cells. One significant way that DNA methylation changes contribute to the cancer phenotype is through the aberrant DNA methylation of MLH1. Specifically, the hypermethylation of the promoter regions of MLH1 inhibits transcription of the MLH1 gene, resulting in suppressed expression of the protein. Inactivating MLH1 often involves the hypermethylation of CpG islands in its promoter, leading to microsatellite instability (MSI). This instability is a genetic hallmark for many cancers. Furthermore, this contributes to the pathogenesis of different types of cancers because the DNA methylation of MLH1 leads to genomic instability, which hinders the cell's ability to repair DNA and can potentially lead to tumor formation (2).

Another prominent promoter region whose epigenetic status is associated with cancer development is that of the interleukin-1 receptor-associated kinase 3 (IRAK3) gene. According to one study, aberrant IRAK3 DNA methylation was identified as a driving epigenetic factor in cancer development, and its promoter was often found to be hypermethylated in cancers. The hypermethylation of IRAK3 caused its expression to be suppressed in cancers, such as colon adenocarcinoma. IRAK3 normally inhibits many pathways vital for the survival of cancer cells, including the NF-kB, STAT3, and MAPK pathways. As a result, IRAK3 typically suppresses the growth of cancer cells. In experimental settings, hypermethylation of IRAK3 in non-tumorigenic cells increased cancer cell colony formation, suggesting increased proliferation of cancer cells. Conversely, overexpressing IRAK3 in cancer cells reduced the cell's ability to support cancer development, thereby inhibiting it (11).

Hypomethylation, defined as unmethylated CpG sites in a sequence where it is normally methylated (27), is the second most common type of DNA methylation abnormality that plays a role in many diseases, including cancer (1). CpG DNA methylation typically takes place in intergenic regions of DNA, which consist of long or short patterns of DNA or RNA (repetitive elements), and in DNA sequences that can change their locations within a genome (transposable elements). As a result, hypomethylation of these regions could cause abnormal gene expression. For example, DNA methylation of long interspersed nuclear element 1 (LINE-1) is vital, as inappropriate LINE-1 activation has a role in processes like the deletion of tumor suppressor genes (11). LINE-1 is an example of repetitive, long interspersed nuclear fragments of DNA. Consequently, hypomethylation of a CpG island in the LINE-1 retrotransposon can result in a

more accessible chromatin structure in associated genes, such as the MET proto-oncogene, thus potentially causing oncogenes to be activated. Activation of these oncogenes could subsequently lead to cancer development (11).

LINE-1 hypomethylation is also associated with the spread of cancer through the lymphatic system to lymph nodes in glandular prostate cancer. Furthermore, hypomethylation in DNA repeats such as LINE-1 is correlated with tumor progression and severity. The hypomethylation of repeating units called satellite DNA, such as centromeric and juxta-centromeric satellite DNA, can be a marker of recurrent cancer and mortality from cancer (2). Moreover, it is likely that the hypomethylation of LINE-1 increases LINE-1 activity due to increased expression, causing increased activity of its encoded proteins, ORF1p and ORF2p, in cancer cells. While ORF1p and ORF2p are not typically expressed in normal somatic tissues, they can be activated in cancerous tissues. Furthermore, high ORF1p expression is associated with many specific cancer characteristics, such as distant metastasis, where cancer spreads from the main tumor to other parts of the body, often via the lymphatic system to lymph nodes. However, it is also important to note that the expression of ORF1p varies across different types of cancer. This suggests that for different types of cancers, ORF1p expression may not be a consistent factor in the regulatory mechanisms of cancer. For example, cancers in the bladder, head, neck, lung, and colon are often associated with the overexpression of ORF1p, whereas renal, liver, and cervical cancers are associated with little to no expression of ORF1p. Overall, this suggests that there are a multitude of factors involved in regulating ORF1p in the context of cancer development, possibly including histone modifications or other post-translational modifications (2).

Role of Histone Acetylation in Cancer Development

Another epigenetic mechanism that can lead to cancer is the disruption of normal histone acetylation and deacetylation. Histone acetylation, specifically at lysine residues such as H4K15 (and many others), generally promotes active transcription of genes. Dysregulations in histone acetylation levels, including both hypoacetylation and hyperacetylation at inappropriate loci, can cause aberrant expression of tumor suppressor genes and oncogenes. As a result, this dysregulation is often correlated with many types of cancer and the progression of those cancers (30). Furthermore, histone acetyltransferases (HATs) can play roles as oncogenes as well as tumor suppressors, depending on the context. Consequently, the dysregulation of HATs such as EP300 and CBP (CREBBP) is associated with various cancers. This is because dysregulation of these HATs affects their ability to acetylate both histones and non-histone proteins, including important regulatory proteins like p53 (which itself functions as a tumor suppressor). These alterations can disrupt critical cell functions such as apoptosis, thereby contributing to the tumorigenesis of the cell (30). Specifically, the loss of function of the tumor protein p53 (encoded by the TP53 gene), a transcription factor located in the nucleus of the cell, is common in around 50% of solid human cancers.

Indeed, the disrupted function of the p53 pathway can result in various downstream effects, including, in some contexts, the activation of pathways like the nuclear factor κB (NF-κB) pathway. The resulting activation of the complex NF-κB pathway can increase cancer cell survival (18). However, the interactions between different signaling pathways regulating cell survival in cancer are not limited to the ones mentioned above; in fact, there are many other examples that indicate the important role of p53 and NF-kB in promoting cancer progression (3).

Histone deacetylation also plays a crucial role in cancer progression. Histone Deacetylase 1 (HDAC1), for example, removes acetyl groups from histone proteins. Specifically, HDAC1 can catalyze the reaction to remove acetyl groups from lysine 27 of Histone H3 (H3K27ac) at the promoter region of genes like STAT1. The deacetylation of H3K27ac by HDAC1 can alter chromatin structure such that the immune response of cells against tumors is suppressed. In other words, the deacetylation of this histone mark can contribute to an immunosuppressive microenvironment. This is consequential because cells like Glioma Stem-like Cells (GSCs) which is a subset of cells within brain tumors that encourage tumor growth, can thrive in the immunosuppressive microenvironment potentially created or maintained by HDAC1 activity. Such an immunosuppressive microenvironment allows GSCs to survive and continue proliferating, thus promoting cancer progression (3).

CONCLUSION

Aging involves a decline of body organs and generally increases susceptibility to age-related diseases. In our world today, there is a growing number of elderly individuals. As a result, people have become increasingly interested in not only living longer but also maximizing the quality of their lives and their health for as long as possible. It has also become a greater concern for

governments to ensure the population ages well, as a larger elderly population could place greater strain on societal systems like pensions.

Epigenetic changes play a fundamental role in the aging process and significantly contribute to the development of age-related diseases such as cancer. While various aging theories have provided different explanations for the biological decline associated with age, the growing emphasis on epigenetic modifications—such as DNA methylation and histone acetylation—sheds new light on the molecular mechanisms underpinning both aging and oncogenesis. As discussed, aberrant DNA methylation patterns, including the hypermethylation of tumor suppressor gene promoters and the hypomethylation of oncogenes or repetitive elements, play a significant role in promoting tumorigenesis in older populations. Similarly, aberrant histone patterns have comparable oncogenic effects. These changes reflect how aging and cancer are deeply interconnected at the epigenetic level.

Recent studies strongly support the epigenetic theory of aging, showing, for instance, that epigenetic reprogramming can reverse certain age-related changes and restore youthful cell functions in experimental models. This theory has significant implications for understanding and treating age-related diseases, particularly cancer, which is heavily influenced by epigenetic factors. Indeed, as people age, their susceptibility to cancer increases, highlighting the need to further examine cancer through an epigenetic lens (18). Recognizing the epigenetic nature of aging and cancer thus increases the possibilities for developing innovative therapeutic strategies aimed at modifying the epigenome for therapeutic purposes. Already, by analyzing cancer from an epigenetic perspective, researchers have identified potential strategies to target age-related diseases like cancer (30). For instance, DNA methyltransferase inhibitors (DNMTis) have emerged as promising cancer treatments. DNMT1 and DNMT3 are key enzymes involved in the methylation of genes and have been linked to various cancers; consequently, targeting these enzymes with DNMTis has gained traction as a potential approach to cancer therapy (12). Histone Deacetylase Inhibitors (HDACis), mentioned in the abstract, also represent such therapeutic approaches targeting epigenetic machinery. Prominent examples of FDA-approved epigenetic drugs include the DNMT inhibitor Azacitidine, used to treat myelodysplastic syndromes, and the HDAC inhibitor Vorinostat, approved for cutaneous T-cell lymphoma. Other agents like Decitabine (a DNMTi) and Romidepsin (an HDACi) further illustrate the clinical translation of these epigenetic concepts.

The possibility of reversing or preventing detrimental epigenetic alterations, as demonstrated in recent animal and cell culture studies, offers a promising avenue for mitigating the effects of aging and reducing cancer risk in the elderly. Future research focused on these epigenetic therapies holds immense potential for improving health outcomes in our aging population. Ultimately, understanding the epigenetics of biological aging helps us better understand age-related diseases and underscores the importance of interventions that address the root epigenetic causes of these conditions. Interventions that target the underlying epigenetic mechanisms of aging and cancer could therefore play an important role in enhancing the health and quality of life for an aging global population.

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DECLARATION OF CONFLICT OF INTERESTS

The author(s) declare that there are no conflicts of interest regarding the publication of this article.

REFERENCES

1. Balducci L & Extermann M. Management of cancer in the older person: A practical approach. *The Oncologist*. 2000; 5 (3): 224-237. https://doi.org/10.1634/theoncologist.5-3-224
2. Berdasco M & Esteller M. Aberrant epigenetic landscape in cancer: How cellular identity goes awry. *Dev Cell*. 2010; 19 (5): 698–711. https://doi.org/10.1016/j.devcel.2010.10.005
3. Berdasco M & Esteller M. Genetic syndromes caused by mutations in epigenetic genes. *Hum Genet*. 2013; 132 (4): 359-383. https://doi.org/10.1007/s00439-013-1271-x
4. Cancer Research UK. (n.d.). Age and cancer. Available from: https://www.cancerresearchuk.org/about-cancer/causes-of-cancer/age-and-cancer (accessed on 2025-05-01)
5. Chilton WL, O'Brien BJ & Charchar FJ. Telomeres, Aging and Exercise: Guilty by Association? *Int J Mol Sci*. 2017; 18 (12): 2573. https://doi.org/10.3390/ijms18122573
6. Elsevier. (n.d.). Epigenome. In ScienceDirect Topics.

Available from: https://www.sciencedirect.com/topics/neuroscience/epigenome (accessed on 2025-05-01)
7. Fang R & Moss TJ. DNA methylation in aging and cancer. *Nat Aging*. 2021; 1 (1): 12-26.
8. Feinberg AP. Epigenomics reveals a functional genome anatomy and a new approach to common disease. *Nat Biotechnol*. 2010; 28 (10): 1049–1052. https://doi.org/10.1038/nbt1010-1049
9. Fraga MF & Esteller M. Epigenetics and aging: The targets and the marks. *Trends Genet*. 2007; 23 (8): 413–418. https://doi.org/10.1016/j.tig.2007.05.008
10. Franklin MA. Epigenetic inheritance in mammals: Evidence for the impact of adverse environmental effects. *Neurobiol Dis*. 2010; 39 (1): 61–65. https://doi.org/10.1016/j.nbd.2009.11.012
11. Frontiers in Cell and Developmental Biology. Epigenetic regulation in aging and age-related diseases. *Front Cell Dev Biol*. 2020; 8: 657.
12. Frontiers in Pharmacology. Epigenetic drugs in aging and age-related diseases. *Front Pharmacol*. 2022; 13: 1072651.
13. Gibney ER & Nolan CM. Epigenetics and gene expression. *Heredity*. 2010; 105 (1): 4-13. https://doi.org/10.1038/hdy.2010.54
14. Horvath S. DNA methylation age of human tissues and cell types. *Genome Biol*. 2013; 14 (10): R115. https://doi.org/10.1186/gb-2013-14-10-r115
15. Jones MJ, Goodman SJ & Kobor MS. DNA methylation and healthy human aging. *Aging Cell*. 2010; 9 (6): 922-934.
16. Li Y, Chen X & Lu C. The interplay between DNA and histone methylation: Molecular mechanisms and disease implications. *EMBO Rep*. 2021; 22 (5): e51803. https://doi.org/10.15252/embr.202051803
17. López-Otín C & Kroemer G. Hallmarks of health. *Cell*. 2019; 181 (1): 1–3.
18. López-Otín C & Kroemer G. Hallmarks of aging: An expanding universe. *Cell Metab*. 2020; 32 (2): 220-233.
19. Lu Y, et al. Reprogramming to recover youthful epigenetic information and restore vision. *Nature*. 2020; 588 (7836): 124-129. https://doi.org/10.1038/s41586-020-2975-4
20. National Human Genome Research Institute. (n.d.). Epigenome. In Genetics Home Reference. Available from: https://www.genome.gov/genetics-glossary/Epigenome (accessed on 2025-05-01)
21. National Institute on Aging. (2000, April 1). Biology of aging. Available from: https://www.ncbi.nlm.nih.gov/books/NBK10041 (accessed on 2025-05-01)
22. National Institute on Aging. (2020, September 10). Some signs of aging can be seen from the outside. In Biology of Aging. Available from: https://www.ncbi.nlm.nih.gov/books/NBK563107 (accessed on 2025-05-01)
23. Reik W & Dean W. Back to the future: Epigenetic reprogramming to rejuvenate aging cells. *Cell*. 2022; 185 (1): 1-3.
24. Smith JM. Lectures on Senescence - I. The causes of ageing. *Proc R Soc Lond B Biol Sci*. 1962; 157 (966): 115-127. https://doi.org/10.1098/rspb.1962.0065
25. Smith ZD, Hetzel S & Meissner A. DNA methylation in mammalian development and disease. *Nat Rev Genet*. 2025; 26 (1): 7-30. https://doi.org/10.1038/s41576-024-00760-8
26. Sen P, Shah PP, Nativio R & Berger SL. Epigenetic mechanisms of longevity and aging. *Cell*. 2016; 166 (4): 822–839. https://doi.org/10.1016/j.cell.2016.07.050
27. SpringerLink. (2017). Epigenetics. In Encyclopedia of Neuroscience. Available from: https://doi.org/10.1007/978-3-642-16483-5_2923 (accessed on 2025-05-01). https://doi.org/10.1007/978-3-642-16483-5_2923
28. United Nations Department of Economic and Social Affairs. (2023). World social report 2023: Chapter key messages. Available from: https://www.un.org/development/desa/dspd/wp-content/uploads/sites/22/2023/01/WSR_2023_Chapter_Key_Messages.pdf (accessed on 2025-05-01)
29. World Health Organization. (n.d.). Addressing the needs of ageing populations. Available from: https://www.who.int/westernpacific/news-room/feature-stories/item/addressing-the-needs-of-ageing-populations (accessed on 2025-05-01)
30. Zhang W & Xu J. DNA methyltransferases and their roles in tumorigenesis. *Biomarker Res*. 2017; 5: 1. https://doi.org/10.1186/s40364-017-0081-z