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REVIEW ARTICLE

Epigenetic alterations—The silent indicator for early aging and age-associated health-risks

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Abstract

Aging is the process of gradual physiological deterioration till death and this process perpetually reduce the functionality of an individual. To address the rationale and provide geriatric care, the constant target of geroscience is to identify reliable biomarkers for aging. Over the past decades, diversified advancements in epigenetic studies crescively support the fact that the accumulation of epigenetic changes accompanies the process of aging. A growing number of studies have suggested that alterations occur through three fundamental mechanisms like methylation of DNA, histone protein modification, and production of non-coding microRNAs. Each of these changes occurs silently and provokes alterations in the circumstantial expression of genetic material without altering the underlying gene sequences. The changes in gene expression due to epigenetic alterations are suggested to be the cause of early aging and the onset of age-related health risks. This review would attempt to give an integrated overview of epigenetic changes related to aging and age-associated health risks. This review also discussed epigenomes influencing early aging and factors modulating it. Since epigenetic changes are reversible, early identification of epigenetic markers can be a hope for future geriatric medicine. Finally, this review emphasizes the identification of blood-based epigenetic biomarkers in order to enlighten the future scope for therapeutic intervention to slow down the aging process.

KEYWORDS
aging, DNA-methylation, epigenetics, histone-modification, MiRNA

1 | INTRODUCTION

The fate of any living organism passing through the period of growth to maximum fitness and attain sexual maturity and then gradual decline of functional mobility with loss of molecular fidelity can be termed as the process of aging. It is a time-dependent physiological deterioration of any living entity followed by an inevitable drop into non-functionality. Pragmatically, the age we calculate by the passing years since birth is called chronological age which is different from the biological age of an individual and we celebrate it each year.[1] On contrary, our biological system is based on cells, and cells will not celebrate as they undergo programmed death after preserving a certain period due to the unavailability of nutrients, and DNA damage. Over the period of lifespan, cellular differentiation, proliferation, and maturation occur followed by apoptosis and these synchronizations get out of balance with age. This reciprocates to the consequences of diseases like cardiovascular disease, metabolic syndromes, neuro-cognitive disorders, etc. Therefore, a common phrase can be used that "aging is the underlying cause of every disease".

Often "aging" is used to represent a state of older phase while in gerontology it is a process that happens over a period with the accumulation of several minute changes depending on the genetic, as well as environmental facets. Thus, in geroscience defining aging biomarkers is one of the major targets.[2] All together nine hallmarks of aging have been discovered including alteration in intercellular communication, deregulated nutrient sensing, exhaustion of stem cells, cellular senescence, increase mitochondrial dysfunction, marked loss of proteostasis, attrition of telomere length, epigenetic modulation, and genomic instability.[3] Several theories had been proposed based on these biomarkers and were widely accepted but no single theory was enough to satisfy all the rationales behind the aging mechanism. Genetic predispositions are the key regulators of aging and have been vigorously evolving over the last few decades.[4] Another concept that influences gene expression without changing the underlying sequences, called epigenetic changes, also come into play in past decades. Epigenetic changes are the ensemble process that encompasses the cumulative outcome of environmental factors, behavior, lifestyle, and psychological status of an individual and altered gene expression.[5] Studies have reported that the chance of genetic influence in the human lifespan variation is nearly 20% to 30% and remaining of the variation is presumably by the influence of environment, diet, lifestyle, and other stochastic events.[6–8] Though the reasons behind successful aging and longevity are poorly understood but the fact of epigenetic changes is widely accepted.

Three fundamental mechanisms include methylation of DNA, modification in the core histone protein, and synthesis of non-coding miRNA contribute towards the age associated epigenetic alterations. Evidences are there to support the fact that each epigenetic change can surpass the next during cell division due to its heritable nature and it is reversible because epigenetic changes do not cause the alteration in the gene sequence.[9,10] Though it does not cause alteration, epigenomes provide the functional stability to chromosomes for carrying that information, and hence genotype reflects the phenotype of an individual.[11,12] As the genome is a pre-programmed repository for the expression of appropriate sets of gene, epigenomes are candidate memories of individuals' lifestyles and environment. Thus, they interchangeably express and carry the information.[13] A growing number of studies interpreted these epigenomes as a potent cause of diseases. Andrew P. Feinberg in his review clearly defined "epigenetic disease". The word "epigenetic disease" represents the disease caused by faulty epigenomes that can include methylated DNA, acetylated histone, and other changes.[14] These changes accumulate throughout one's lifespan and express differently. Hence epigenetic alterations are one of the nine hallmarks of aging-related changes. Since epigenetic alterations accumulate over the period without any noticeable phenotypic changes, their effect remains silent for decades until any disease thrives. In this review, we highlighted those epigenetic changes influencing aging and we emphasize age-related diseases that are caused by epigenome. Further, we gave a brief account of the early detection of epigenetic changes so that they can be identified at the primary stage.

1.1 | Concept of epigenetic alterations

The term epigenetics arises from the fact that is above or beyond the genetic code. According to discoveries, the human body comprises over 200 cell types, but each cell has the same DNA or precisely the same heritable information. Instead that each of them behaves differently and their functions are unique. Epigenetic alterations are an orchestrated event that regulates these distinct behaviors by the transcriptional output of their respective codons.[9] C. H. Waddington, a British embryologist introduced the term "epigenetics" in the year 1942, from the context of "epigenesis" which was a conceptualized form of interaction between genes and surroundings to give a phenotypic change. This is similar to the metamorphosis of an organism in biological development.[15] In the past eight decades, this term had been utilized in divergent biological interpretations, but its underlying mechanism is quite homogenous. The changes in gene expression occurred mainly through the modification at the chromatin level including core histone octamer. Mainly cysteine-rich regions of DNA molecules got modulated either by substitution or elimination of specific hydrocarbon groups. These changes can either be spontaneous or influenced by endogenous or exogenous factors. All these changes can be enumerated into three mechanisms including DNA methylation, Histone modification, and production of non-coding micro RNAs.

1.2 | DNA-methylation

Central dogma of molecular biology suggests methylation at three levels including DNA, RNA, and protein. Considering DNA-methylation in mammals, occurs mostly at CpG sites of dinucleotide molecules by different methyltransferases and in molecular gerontological research, it has been a valuable tool to assess the aging process.[16] It is a well-discovered epigenetic alteration, but the mechanism and specificity are still unclear.[17] Methylation occurs due to the transfer of a methyl group from SAM (S-adenosyl methionine) to the 5th carbon of cytosine molecule to form 5-methylcytosine, by the catalyzing action of three DNMTs (DNA-methyltransferases) namely DNMT1, DNMT3a, and DNMT3b.[18] According to developmental biology, these patterns of global demethylation occur twice in a mammalian life cycle, one during gametogenesis and another during the pre-implantation phase.[19] CpG methylation is brought to restrict gene transcription as it interferes with the transcriptional machinery. Thus, the expression of that gene alters and brought to phenotypic changes.

Acceleration of age has an intense effect on DNA methylation status which can also be representative of health condition of an individual. Hypomethylation is marked at the CpG region with aging while hypermethylation is also seen at CpG islands with aging and in cancer. Based on these findings Hovarth et al. and Hannum et al. in the year 2013 consecutively proposed an epigenetic clock for predicting aging. Epigenetic clocks mostly are based on DNA-methylation status from peripheral blood sample data including Hannum but in contrast, Hovarth's clock was based

upon integrated data from multiple tissues like blood, brain, embryonic stem cells, etc.[20,21] In a study, Nicola et al. had examined the relationships between two epigenetic clocks with aging. They successfully concluded that predicted age and chronological age of those individuals are highly correlated with Pearson's r value of 0.93 to 0.97.[22] However, predicting age and age-associated diseases with a single marker like DNA methylation has yet to be discovered but it is a reliable predictor.

1.3 | Histone-modification

Eukaryotic genome is packed inside the chromosome in a highly organized order chromatin structure. Deoxyribonucleic acid wraps around the histone octamer comprising two sets of four histone proteins namely H2A, H2B, H3, and H4. This packaged unit form the functional unit of chromatin called nucleosome which contains approximately 147 base pairs.[12] Histone octamer inside the nucleosome structure undergoes modification which can either cause activation or repression of gene expression. This modification can be of two types, covalent and non-covalent, depending upon the expenditure of ATP and the bond. Covalent modification encompasses the processes like methylation, acetylation, ubiquitination, ADP-ribosylation, sumoylation, and phosphorylation, of amino acid residues of histone proteins. While the non-covalent modification is an ATP-dependent complex process of chromatin remodeling. Another term euchromatin modification had been introduced where modification is coherently related to the transcription mechanism. It ensures the acetylation of H3, and H4 histone proteins, along with di-methylation and tri-methylation of H3 protein.[8]

Different histone methyl transferase (HMTs) class enzymes are involved in the mechanism of histone protein methylations depending on the amino acid residues. Increase methylation of lysine residues of H4 protein called H4K20Me3 and it is found to be a lethal cause for HGPS (Hutchinson Gilford Progeria Syndrome). HGPS is associated with premature aging where some debilitating phenotypes of older age are seen including sarcopenia, alopecia, loss of subcutaneous adipocytes, etc. Studies showed similar changes in above 80 years old individuals.[23] Acetylation is another process that is frequently marked as a biomarker for aging. Histone protein acetylation is catalyzed by Histone Acetyltransferase (HAT), and parallelly deacetylation process is catalyzed by Histone Deacetylase (HDACs). These modifications of amino terminals of histone proteins work post-transcriptionally and are believed to influence the accessibility and expression of respective genes. Often, this phenomenon is referred to as "The Histone code hypothesis".[5] ATP-dependent histone modification occurs through non-covalent modulation of chromatin which is called as chromatin remodeling. This process involved in nucleosome positioning concern to the histone-DNA interactions. ATP-dependent chromatin remodellers are the multi-subunit complexes where ATPase is an integral catalytic center. ATPase center conserves three complexes such as SWI/SNF, M2/CHD, and ISWI with a catalytic core domain. Over-expression of BRG1, one of the SWI/SNF complexes, induces cellular senescence has been reported while BRM another SWI/SNF ATPase are found to regulate aging in the rat liver.[5,23] Accumulation of these minute modifications of histone octamer over the year can potentially alter the gene expression. The altered expression is often related to the onset of early aging as well as age-related health issues.

1.4 | Non-coding RNA production

The production of non-coding ribonucleotides becomes an evident modulator for epigenetic changes. microRNAs are one of endogenous non-coding RNAs that have the capability to silence gene expression through post-transcriptional modification.[24] Initiation of biogenesis of miRNAs occurred by RNA polymerase II. At the initial phase 70 nucleotide long pri-miRNA is formed which is then processed to pre-miRNA by DROSHA an RNase enzyme. Exportin-5 mediate this action of export from the nucleus to the cytoplasm. In the cytoplasm, DICER another RNase enzyme cleaves the miRNA duplex to form mature 18 to 22 nucleotide long mature miRNA.[25] Once the miRNA is released, it binds with complementary base pairs of target mRNA at 3'UTR (Untranslated region) and causes repression of expression either by mRNA degradation or producing different translation proteins. A single mature miRNA can target more than one mRNA, on the other side one mRNA can be a binding site for multiple miRNAs.[26]

This non-coding ribonucleotide or miRNA was first discovered in C. elegans where lin-4 miRNA was found to be a potent regulator of development. miRNA lin-4 is evident to modulate nematodes' lifespan by acting through the IIS (insulin/IGF-1 signaling) pathway of senescence. Likewise, miR-1, miR-320, and miR-206 by targeting IGF-1 while miR-216a, miR-217, and miR-21 mainly target PTEN to influence the IIS pathway in mammals. Shreds of evidence are there to support the fact that miRNAs also influence other aging pathways like mTOR, AMPK, and sirtuin pathways.[24] In 2018, in a systematic review, miR-125b has been reported for regulating MAPK (Mitogen-Activated Protein Kinase) in association with Alzheimer's dementia related to early-life stress.[27] Thus, altered expression of miRNAs can be a valuable marker for early aging and age-related diseases like specific carcinoma, atherosclerosis, Alzheimer's, and others. Upregulation of miR-124 has been reported to be a target marker for aged skin and squamous cell carcinoma while overexpression of miR-26a can be a potential predictor of non-HTN intracerebral hemorrhage.[28,29] Several miRNAs are continuously evolving as well as supporting age-related phenotypic changes and diseases.[26] In the past decades, the identification of miRNAs and their mechanisms to mitigate the aging process added a new dimension to molecular gerontology (Figure 1).

2 | EPIGENOMES AND AGING

Epigenome refers to congregation of chemical changes that can pass the instruction to the genome through Transgenerational

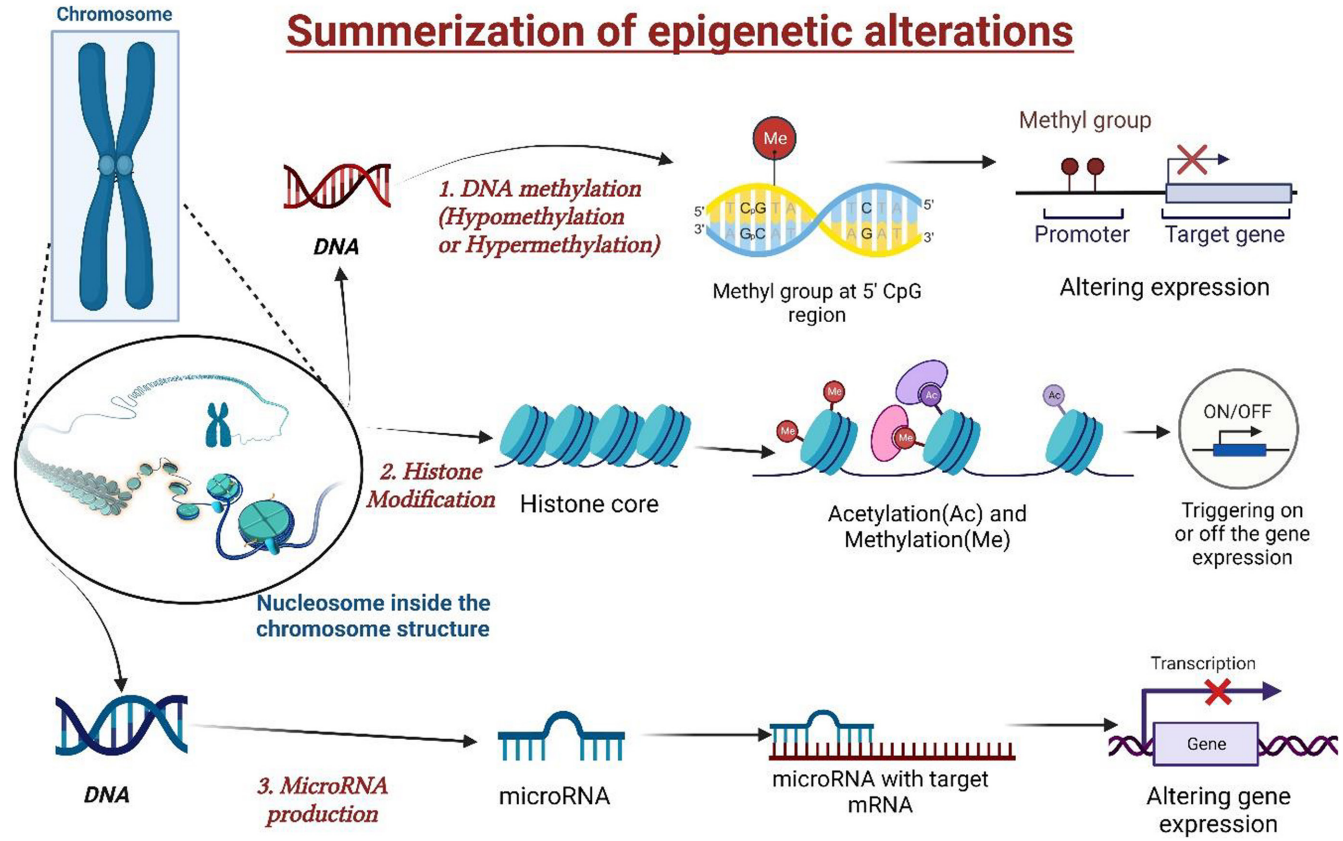

FIGURE 1 Schematic diagram of epigenetic alterations. (1) DNA methylation i.e., the substitution or elimination of methyl group mostly at 5' CpG region. (2) Histone modification i.e., addition of methyl, acetyl, and other hydrocarbon groups to histone proteins. (3) Production of microRNA from DNA. Created with BioRender.com

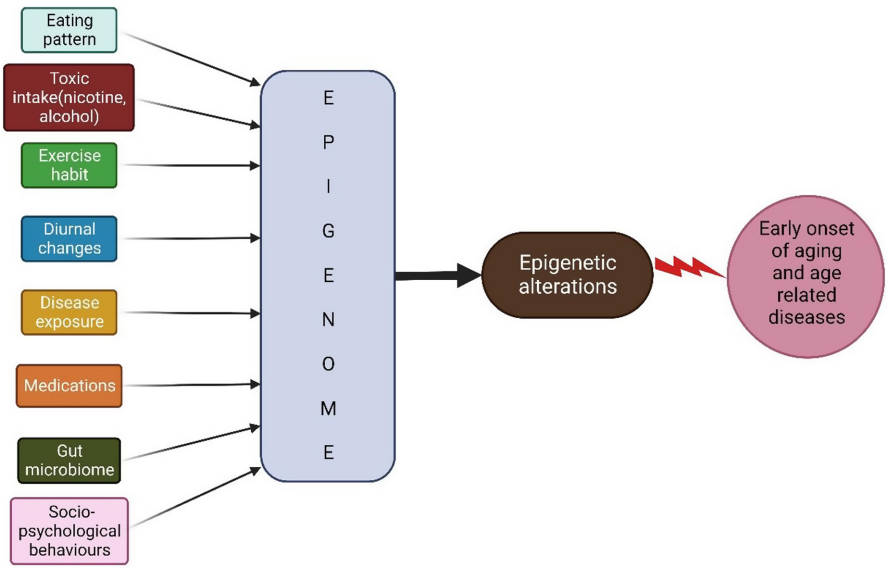

FIGURE 2 Flow diagram showing factors affecting epigenome causing early onset aging. Created with BioRender.com

standard epigenetic inheritance. Epigenome comprises different chemical compounds along with proteins that cause turning "on or off" gene expression by attaching to DNA molecules. Once they are attached to DNA, that respective genome is referred to as marked. And inherently this marked genome passes down through the cell to the generation to next. Although, these changes are heritable, lifestyle, dietary patterns, environmental components, behavioral and psychological status can induce epigenomic changes. Excessive smoking habits, unhealthy lifestyles, imbalanced diet, stress, psychological depression, societal changes, diurnal or weather changes, and all other surrounding factors can accentuate epigenomic changes and lead to early damage of DNA.

These changes correspond to the senescence cells, and the onset of early aging with diseases.[30] Over the past year, researchers vigorously addressed micronutrients that play major roles in our body building components, henceforth they have the probability to influence epigenomes. Micronutrients including zinc, magnesium, vitamin C, vitamin D3, a range of vitamin B complex, thiamine, pyridoxine, and others have the potential to modulate epigenomes and thereby age-related consequences as these micronutrients are coherently involved in regulating metabolism, neurotransmitter generation, bone density, plasma membrane potential and others.[31] A pilot RCT in the year 2021 showed the potential of dietary and lifestyle intervention in reversing the epigenomic changes among 43 healthy males belonging to the age group 50–72 years.[32] Thus, the consequences of faulty epigenomes can be potentially treated back to a healthy status (Figure 2).

3 | INDICATION FOR AGING AND AGE-RELATED DISEASES

Though aging cannot be ceased, aging markers can be identified and thereby therapeutic as well as nutritional intervention can slow down the process or its related health risk. As we know aging itself is not a disease but due to senescence, cells lost their proliferative and differentiating capability which further leads to the occurrence of diseases. Cardiovascular diseases are most commonly associated with age, followed by diabetes, Alzheimer's, Parkinson's, and specific type of cancer also. Early detection of aging biomarkers can be a preventive measure for clinicians. Tissue-specific biomarkers are restricted in certain study as it depends on the live human subject, but blood-based biomarkers can be detected by peripheral blood sample, and it is easily accessible. The Discovery of RT-PCR added leverage to the identification of blood-based epigenetic markers, and it can be a potent indication of early aging and age-related diseases if detected in the early stage. DNA hypermethylation is a valid indication for certain type of tumorigenesis.[33] Studies on ischemic heart disease found hypomethylation of DNA is highly related and they depicted the global loss of DNA methylation as the indication for atherosclerosis.[34] In 2012 Gary C. et al. reported global hypomethylation for breast cancer and histone methylation.[35] A longitudinal study in 2019 was done on 11,461 participants and this study concluded the association between blood-derived DNA methylation with the risk of CHD (Coronoary Heart Disease) across a diverse population and hence methylation status as an informative tool.[36] While in the case selective colon cancer, hypermethylation in the downregulated genes has been identified.[37]

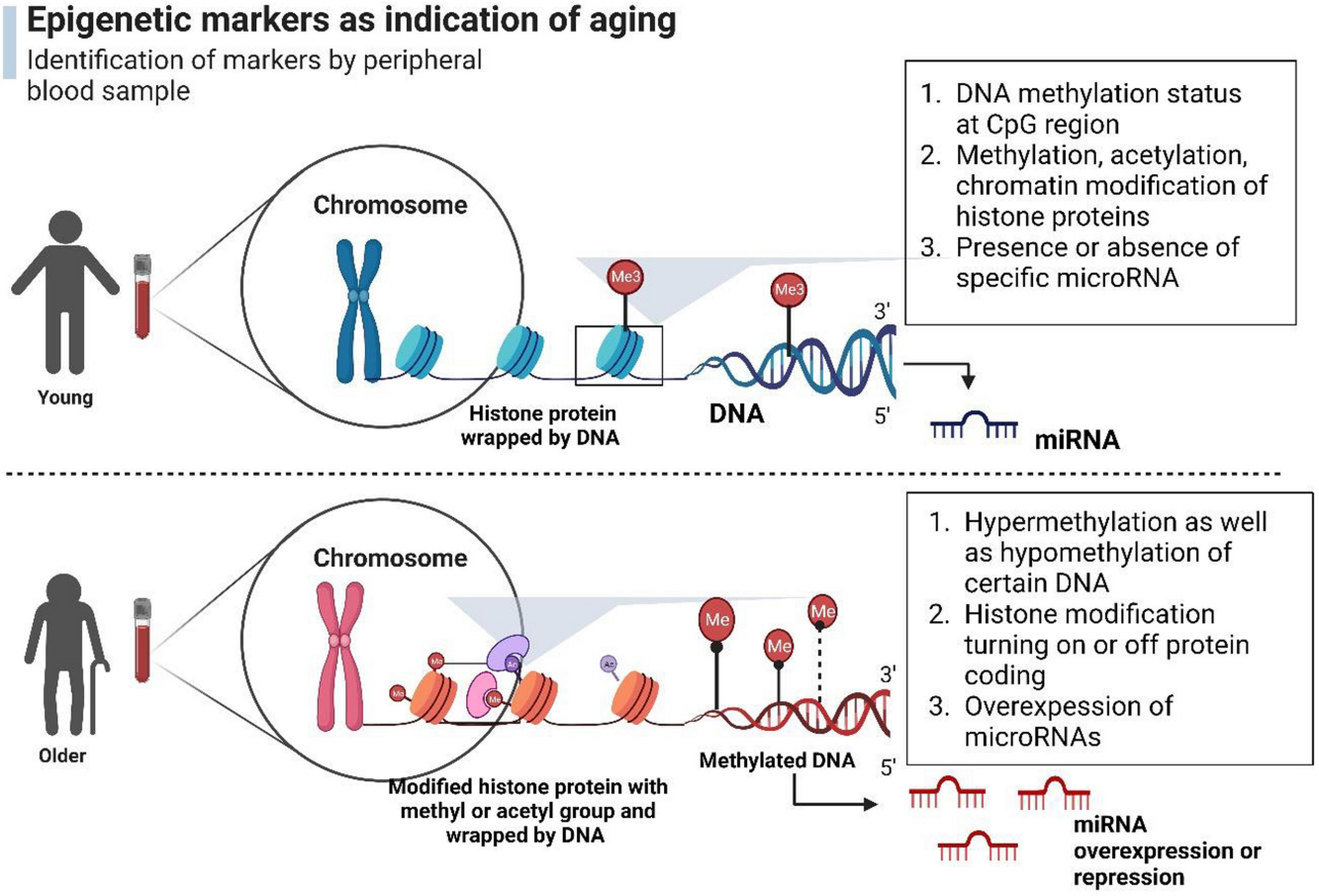

FIGURE 3 Overview of identification of epigenetic markers as an indication of aging and age-related health risk. Created with BioRender.com

The accuracy of prediction of early aging and age-related diseases by blood-based epigenetic biomarkers is increasing and the newly developed "next-generation clock" DNAmGrimAge transcends the "first-generation clocks". Using this accuracy, intervention studies are implemented where diet and physical activity showed to slow down the DNA methylation status.[38] The pattern of epigenetic markers is not homogenous for every case, that is what makes two identical twins with different characteristics. Thus, identifying the changes for each case can have the potential to build a database. This database repository can be further utilized in predicting the disease (Figure 3).

4 | CONCLUSION

The acquisition of knowledge for epigenetic changes is limitless. As nature and nurture differ, the outcome of every epigenetic change also differs. The detection of epigenetic markers is not only to identify aging but also to identify the onset of age-related diseases. This is an integrated informative review that briefly discussed all the discovered epigenetic changes along with the factors or epigenome which potentially influence epigenetic modulation and thereby cause health-related menace. Since we, human beings are constantly facing different environmental experiences, our genome is also getting different sets of epigenomic instructions which are completely independent and unique.

Multiple shreds of evidence in this review, including methylation at the CpG region, a trace of H4K20Me3, and miR-1 detection have an implicating role in the detection of aging. In this review, we have enlightened a few of the information about hypomethylation and hypermethylation, followed by histone protein modification, and non-coding RNA synthesis, in the aspect of disease conditions. A further systematic review is required to engross the vast research on the epigenome. Current epigenetic studies are becoming a pivotal point of biomedical research in terms of pharmaceutical drug discoveries and new therapy inventions. By using the reversible nature of epigenetic changes, the implementation of new inventions has a bright future in the field of biomedical research. Interdisciplinary alliances can also enrich age-related epigenetic studies by incorporating computational biology, bio-informatics, and next generation sequences. The universe is vast, and its entity is unbounded. Thus, finding a reason behind successful aging with minimal disease has always been a target and this review can be a seed for further discovery.

AUTHOR CONTRIBUTIONS

Ms. Poulami Dhar—Drafting and design of the article. Dr. Shailaja S. Moodithaya—Concept and revision of the article. Dr. Prakash Patil—Revision of the article.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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