Epigenetic Modifications, Elderly Cardiovascular Disease

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Contributor: Mojgan Gharipour, mona aminibaghbadorani

The rate of aging has increased globally during recent decades and has led to a rising burden of age-related diseases such as cardiovascular disease (CVD). At the molecular level, epigenetic modifications have been shown recently to alter gene expression during the life course and impair cellular function. In this regard, several CVD risk factors, such as lifestyle and environmental factors, have emerged as key factors in epigenetic modifications within the cardiovascular system.

Keywords: epigenetics ; older adults ; cardiovascular disease ; aging ; lifestyle ; environment ; physical inactivity ; diet ; nutrients ; caffeine ; alcohol consumption

1. Introduction

The World Health Organization (WHO) predicts that the worldwide proportion of individuals aged 65 and older will double between the years 2000 and 2050, from the current 6.9% to 16.4% [1]. The older adult population in 2050 will be 16 times larger than that in 1998, with the male-to-female ratio of centenarians falling to almost 1:4 [2]. Although increasing the population's longevity is considered an accomplishment of healthcare systems, aging has been associated with a progressive decline in several physiological processes and increased risk of chronic conditions [3]. Aging increases the burden and prevalence of many common diseases such as cancers, diabetes, and cardiovascular disease (CVD). CVD is the leading cause of death later in life [4]. Aging affects the cardiovascular system as reflected in pathological conditions such as myocardial hypertrophy, changes in left ventricular (LV) diastolic function, diminished LV systolic reverse capacity, increased arterial stiffness, and impaired endothelial function. For example, increasing arterial stiffness leads to myocardial compensatory mechanisms, including LV hypertrophy and fibroblast proliferation, resulting in decreased cardiac output and an increase in fibrotic tissue [5][6][7]. Older adults frequently suffer from various comorbidities and often they have different comorbidities, therefore determining several phenotypes. These various phenotypes are characterized by different frailties as well as different cardiovascular outcomes. Findings from the Registro Politerapie SIMI (REPOSI) registry showed that being male, history of hospitalization, polypharmacy (more than five drugs), lower functional status and fragility, depression, CVD, chronic obstructive pulmonary disease, and urinary tract infection were related with a higher risk of hospitalization in older adults [8]. Moreover, aging is characterized by chronic low-grade systemic inflammation, and is associated with multiple chronic conditions such as ischemic heart disease, heart failure, myocardial infarction, diabetes, lung cancer, osteoporosis, and metabolic syndrome as well as CVD risk factors such as lipid disorders [9][10][11][12]. A study by Li et al., demonstrated that an epigenetic modification in ELOVL fatty acid elongase 2 (Elovl2), a gene whose epigenetic alterations are most highly correlated with age prediction, contributes to aging by regulating lipid metabolism. Impaired Elovl2 function disturbs lipid synthesis with increased endoplasmic reticulum stress and mitochondrial dysfunction, leading to key accelerated aging phenotypes [13].

Consequently, understanding the molecular mechanisms related to CVD throughout the life course could help us to understand what happens during aging in the cardiovascular system. A growing body of evidence suggests that epigenetic modifications may significantly disrupt gene expression routes during the life course, thus affecting the molecular phenotype and function of involved cells [14]. Therefore, in the present review, we discuss the emerging role of epigenetics in CVD among older adults and the potential impact of lifestyle and environmental modifications on preventing deleterious epigenetic changes in this age group [15].

Aging results from the collective effect of molecular and cellular damage over time [16]. A combination of genetic and environmental factors (e.g., diet, smoking, obesity, and stress) affects the aging process [16]. At the molecular level, any changes in gene expression can result in altered cellular and tissue function. For example, aging of the heart is accompanied by changes in the expression of genes encoding proteins that are involved in inflammatory and stress responses that, when exceeding the homeostatic levels, impair cardiac function [17]. These changes can be triggered by

genetic mutations or epigenetic modifications that cause changes in the gene expression profile. Any changes in the structure of DNA, RNA, and proteins throughout life alter their function and may lead to changes in cellular and organ function, leading to various diseases [18][19][20]. Consequently, understanding the molecular processes that contribute to CVD during the life course could provide information on the mechanisms that underlie cardiovascular aging. In the present review, we discuss the emerging role of epigenetics in CVD among older individuals and the possible impact of lifestyle and environment in this population [15].

2. Aging, CVD, and Epigenetic Modification

While cardiac hypertrophy and cardiac fibrosis are considered as the main causes of heart failure, several genes have increased expressions, e.g., Nappa, Nppb, Myh7, and skeletal alpha-actin [19][20][21].

DNA methylation, an epigenetic mechanism that leads to changes in gene expression, is heritable and impacted by aging and various environmental exposures [22]. Levels of DNA methylation, which cluster in specific loci of the human genome, could be used as a marker of biological aging. DNA methylation age (DNAmAge) can provide an estimate of the biological age, and can be used as a tool to estimate “accelerated biological aging” which contributes to several diseases such as diabetes, CVD, and dementia, and, ultimately, mortality risk [20][23][24][25][26][27][28][29][30]. A recent methylome-wide association study conducted on 718 men and women aged between 25 and 72 demonstrated a positive correlation between increased methylation of CpG islands, shores, and shelves with aging [25][31]. Numerous studies have associated DNA hypermethylation with the pathogenesis of atherosclerosis [32][33].

Interestingly, a monozygotic twin study demonstrated that the epigenomes of young monozygotic twins are very similar, but patterns of methylation in monozygotic pairs differ as they age [25]. In this regard, Fraga et al., examined the global and locus-specific differences in DNA methylation and histone acetylation of a large cohort of monozygotic twins and demonstrated that while twins are epigenetically indistinguishable during the early years of life, they exhibited noticeable differences in their overall content and genomic distribution of 5-methylcytosine DNA and histone acetylation as they aged, resulting in overall different gene expression profiles [25]. Specific methylation changes, usually hypermethylation, have been found in the promoter region of genes that are considered protective against atherosclerosis, such as extracellular superoxide dismutase, estrogen receptor α, endothelial nitric oxide synthase, and 15-lipoxygenase [34][35]. McKay et al. , identified the genome-wide DNA methylation changes and the locus-specific CpG alterations taking place during the onset and progression of human atherosclerotic lesions. The methylation of the p66Shc promoter is reduced by different CVD risk factors (i.e., hyperglycemia, ox-LDL), whereas JunD promoter methylation is increased, the latter being particularly evident with aging [36]. Both p66Shc and JunD expression levels are profoundly altered in the circulating endothelial progenitor cells isolated from older adult patients compared to young individuals [37].

Histone methyltransferases are responsible for the methylation of histone lysine and arginine at different sites. Briefly, H3K4 methylation induces gene activation while H3K9 and H3K27 methylation inhibit gene expression. In addition, modification of polymethyl groups on histone lysine leads to different levels of methylation that may have different biological significance. Interestingly, age-related DNA hypermethylation in mesenchymal stem cells (MSCs) is associated with repressive histone marks H3K27me3/H3K9me3 [38], while hypomethylated DNA sequences are powerfully enriched with the active chromatin mark H3K4me1 [39]. Histone modifications such as acetylation of histone 3 at lysine 9 (H3K9Ac) and trimethylation of sirtuins are crucial regulators of the aging process from yeast to mammals [40].

3. Aging, Epigenetic Modification, and Inflammation

The term “inflamm-aging” is a relatively new term added to the medical vocabulary by Franceschi et al., in 2000. It refers to the upregulation of the inflammatory response later in life as a consequence of epigenetic changes with a subsequent systemic low-grade chronic proinflammatory state that underlies most age-associated diseases [41][42]. One of the common effects of aging is the excessive production of inflammatory cytokines and reactive oxygen species (ROS) [43][44][45][46]. ROS production increases with age due to a variety of epigenetic stimuli, including physical, chemical, and biological agents. Oxidative stress occurs as an imbalance between ROS production and the body’s capacity to detoxify the resultant reactive intermediates or repair consequent impairment. ROS is behind endothelial dysfunction, effectively lowering the threshold for many diseases, especially CVD [47]. Oxidative stress increases vascular permeability and promotes leukocyte adhesion as well as an inflammatory response. A low level of chronic inflammation is associated with atherosclerosis, CVD, and diabetes. The immune system produces more proinflammatory cytokines under the regular stimulus accompanying aging. IL-6, TNF-α, and CRP mark the onset of CVD in older adults, and their levels correlate with the severity of left ventricular dysfunction and degree of activation of sympathetic and renin–angiotensin systems. **Table 1** summarizes the most relevant epigenetic changes and inflammation processes in CVD.

Table 1. Summary of the most relevant epigenetics changes and inflammation processes in CVD.

Epigenetic Modifications	Sites	Affected Gene
DNA methylation	KLK10, LIM, LMO, D1D, CD7, CD22, CD27, CD59 and CD82, IL1R2, IL2RA, IL19, IL21R, IL32, GPR21, GPR65, GPR81, GPR84, and GPR171	CRP [48]
	BAF155, Inil, c-Myc, BAF170, Max, NRSF, and Nrf1	IL-6 [49]
	NLRC5 and DTX3L/PARP9, IFN-γ, and ABO	TNF-α [50]
		SIRT1, FoxO3, NF-κB, and p53 [51]
Histone modification	H3K4me3	TNF-α [52], SET1A/B, SET7, MLL1/2, MLL3/4, LL1, and VEGFA [53]
	H3K4me3 and H3K9ac	TNF-α [52]
	H3K9me2	VSMC [54]

CRP is a biomarker of systemic inflammation and a risk factor for the development of inflammation-mediated diseases such as CVD, metabolic syndrome, type 2 diabetes, and hypertension [55][56]. The production of CRP in the liver is triggered by cytokines (e.g., IL-6 which is secreted by macrophages and T cells) in response to inflammatory conditions. CRP level is associated with the epigenetic profile, specifically DNA methylation, which may represent the joint effect of both genetic and environmental factors [57]. Sun et al. , identified over two hundred genes containing CRP-associated DNA methylation sites. The most significant CRP-associated DNA methylation sites are cg07073964, cg09358725, and cg11822932, which are in the KLK10, LIM, and LMO gene loci, respectively. There are several gene families related to the immune system that are enriched in the gene set of CRP-associated DNA methylation. Six immunoreceptor (CD) genes, CD1D, CD7, CD22, CD27, CD59, and CD82, and five interleukin and receptor genes, IL1R2, IL2RA, IL19, IL21R, and IL32, were identified by epigenetic association analysis. The methylation sites in five G-protein-coupled receptor (GPR) gene loci, GPR21, GPR65, GPR81, GPR84, and GPR171, were also found to be associated with CRP [57].

IL-6 is a multifunctional cytokine that plays an important role in the development of ischemic heart diseases. DNA hypomethylation in the IL-6 promoter was associated with an increased risk for coronary heart disease, especially in acute myocardial infarction. Lepeule et al., suggested that differential DNA hypomethylation of the two distinct CpGs in IL-6 may reflect different cumulative effects from endogenous and exogenous exposure factors, and then contribute differently to the susceptibility to coronary heart disease. Transcription factor binding sites (BAF155, Inil, c-Myc, BAF170, Max, NRSF, and Nrf1) were identified for position 1, whereas position 2 was free of the binding sites [58].

TNF-α is a proinflammatory cytokine with pleiotropic effects in human disease and well-characterized pathogenic contributions to inflammatory and autoimmune diseases such as atherosclerosis and type 2 diabetes. Treatment with TNF inhibitors has been shown to lower the risk of cardiovascular disease among patients with autoimmune disease [59]. Altered methylation of CpG loci in the TNF promoter has been associated with TNF-α expression [60][61]. In addition, DNA methylation loci in two genomic regions mapping to NLRC5 and DTX3L/PARP9 changes expression of corresponding genes and alters circulating TNF-α levels. These processes are induced chiefly by interferon γ (IFN-γ) stimulation, Toll-like receptor ligands, and other interferons in response to diverse stimuli such as viral infections [62]. By activating CD8+ T cells via major histocompatibility complex class I proteins, NLRC5 has also been shown to upregulate IFN-γ, creating a positive feedback loop that ensures an effective response to intracellular pathogens [63]. Increased expression of DTX3L-PARP9 has been shown to enhance IFN-γ signaling and therefore host immune response [64]. Recent evidence suggests that DTX3L-PARP9 may also play a key role in vascular inflammation and atherosclerosis. There are associations between TNF-α levels and methylation loci in the α 1-3-n-acetylgalactosaminyltransferase, and α 1-3-galactosyltransferase gene (ABO) [65].

4. Effect of Lifestyle and Environmental Factors on Epigenetic Modification in Older Adults with CVD

A recent genome-wide DNA methylation study with 3096 participants demonstrated that tea and coffee consumption are also associated with altered methylation in two differentially methylated CpG sites (DNAJC16 and TTC17) [66]. Another study reported an association between ω-3 PUFA supplementation and vegetable and fruit consumption and lower

GrimAgeAccel, DNAm PAI-1, DNAm ADM, and DNAm cystatin C which are considered epigenetic age markers enriched for DNA methylation sites that are surrogate biomarkers for blood plasma proteins related to aging [67][68].

Similarly, magnesium and selenium levels may function as potential epigenetic regulators via modulating different signaling pathways [67][68][69]. The possible epigenetic effects of selenium are the modulation of epigenetic information editors, interaction with miRNAs, as well as influence on the metabolism of a carbon, which acts as a methyl donor for DNA methylation [70][71].

Tobacco smoking induces dysregulated DNA methylation in hundreds of CpG sites which are related to the epigenetic clock [72]. Therefore, the epigenetic alterations of smoking and vaping include DNA methylation, microRNA, and non-coding RNA, and research in animals and humans has also reported that the use of electronic cigarettes (vaping) is linked to worse general and respiratory health, similar to effects observed with conventional smoking [73].

It is well established in the literature that ethanol can alter gene expression through epigenetic mechanisms, that is, prolonged exposure to ethanol can alter DNA and histone methylation, histone acetylation, and microRNA expression [74].

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