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Review article

DNA damage response, a double-edged sword for vascular aging

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ABSTRACT

Vascular aging is a major risk factor for age-related cardiovascular diseases, which have high rates of morbidity and mortality. It is characterized by changes in the blood vessels, such as macroscopically increased vascular diameter and intima-medial thickness, chronic inflammation, vascular calcification, arterial stiffening, and atherosclerosis. DNA damage and the subsequent various DNA damage response (DDR) pathways are important causative factors of vascular aging. Deficient DDR, which may result in the accumulation of unrepaired damaged DNA or mutations, can lead to vascular aging. On the other hand, over-activation of some DDR proteins, such as poly (ADP ribose) polymerase (PARP) and ataxia telangiectasia mutated (ATM), also can enhance the process of vascular aging, suggesting that DDR can have both positive and negative effects on vascular aging. Despite the evidence reviewed in this paper, the role of DDR in vascular aging and potential therapeutic targets remain poorly understood and require further investigation.

1. Introduction

The human genome frequently encounters various exogenous and endogenous stimuli, which cause various types of DNA damage that threaten the genomic stability (Jimeno et al., 2019). Human cells are estimated to experience up to 70,000 DNA lesions per day, most of which are single-strand breaks (SSBs). To safeguard genomic integrity and prevent damage transmission to their progeny, cells are equipped with sensitive signaling cascades called DNA damage response (DDR). DDR are pathways that sense, signal, and repair genetic lesions, as well as induce apoptosis or cell senescence when DNA damage is irreparable (Bader et al., 2020). Multiple DDR pathways are activated for the repair of different categories of DNA damage. Each DDR pathway repairs a specific subset of lesions, with a certain degree of overlap among them. Defects in DDR pathways can result in the accumulation of genetic mutations, which can cause various diseases such as premature aging syndromes (such as progeria syndrome) (Liu et al., 2006) and age-related phenotypes (Cheng et al., 2022).

By 2050, the world's population is expected to reach around 9 billion (Meyer et al., 2008), with a significant increases in the over-65 age groups (Barton, 2014, 2005). As people live longer, the prevention and management of age-related diseases have become a global priority. Vascular aging, which refers to age-related changes in the vascular system, is a specific type of biological aging (Lin et al., 2019). As the famous 17th-century physician Thomas Sydenham said, "A man is as old as his arteries". Vascular aging is considered the most important risk factor for the high mortality of cardiovascular diseases (CVDs) and affects many aspects of CVDs, such as their onset, progression and severity. It is estimated that the annual cost of informal caregiving for CVD patients will double from 2015 to 2035 (Dunbar et al., 2018), highlighting the importance of addressing these age-related vascular diseases. To develop novel therapeutic interventions to prevent and treat age-related CVDs in the future, a better understanding of the cellular and biological mechanisms of vascular aging is essential. Recently, growing evidence suggests that DNA damage is a key causal event in vascular aging (Borghini et al., 2013). As a major contributor to detecting DNA

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damage and maintaining genomic stability, the role and mechanism of DDR in vascular aging also attracts the attention of researchers.

In this review, we first summarize the major DDR pathways and the characteristics of vascular aging. Then, we review the current knowledge on the role of DDR in vascular aging and discuss how these findings can offer new opportunities for preventing and treating age-related CVDs.

2. DDR pathways

2.1. The direct reversal pathway

Certain DNA damages that involve modifications to DNA can be directly reversed by single repair proteins without incisions in the DNA backbone, which is known as the direct reversal pathway (Yi and He, 2013). Although only repairing a relatively small set of DNA lesions, the direct reversal process is still attractive for cells because of its simplicity and error-free properties. To date, three major mechanisms of direct reversal pathways have been reported, including UV light-induced photolesions reversed by photolyases, *O*-alkylated DNA damages reversed by O^6-alkylguanine-DNA alkyltransferase, and *N*-alkylated base adducts reversed by the AlkB family dioxygenases (Yi and He, 2013; Fu et al., 2012). After repairing DNA, this group of enzymes is destined for degradation; hence, they are termed "suicidal enzymes" (Souliotis and Kyrtopoulos, 1989) (Fig. 1).

2.2. Mismatch repair (MMR)

The MMR pathway removes base-base mismatches and insertion-deletion mismatches generated during DNA replication to restore the parental genotype (Kunkel and Erie, 2005). In the MMR pathway, the recognition of initial mismatches is followed by the removal of the newly synthesized DNA encompassing the mismatches, the correct re-synthesis of DNA by DNA polymerase δ or ε filling in the nucleotide gap, and then the subsequent joining of 3'-OH and 5'-phosphate in the DNA backbone by DNA ligase. The homologs of MutS and MutL, such as MSH2 and MLH1, are the conserved core proteins in MMR of nuclear DNA mismatches in eukaryotic cells. Deficient MMR leads to the generation of microsatellite instability (MSI), characterized by spontaneous insertion or deletion of nucleotides within repetitive DNA sequences (Jiricny, 1994). Mutated *MMR* genes can be identified in patients with Lynch syndrome, who are predisposed to early-onset multiple cancers of the colon, endometrium, ovary, and other organs (Bonadona et al., 2011) (Fig. 1).

2.3. Base excision repair (BER)

Small base lesions that arise from deamination, oxidation, alkylation, and depurination/depyrimidination are repaired by a highly conserved DDR pathway named BER. These small base lesions do not severely distort the DNA helix structure or obstruct transcription and replication, but they can lead to non-canonical base pairing and the generation of mutations. Therefore, BER contributes to genome integrity by repairing

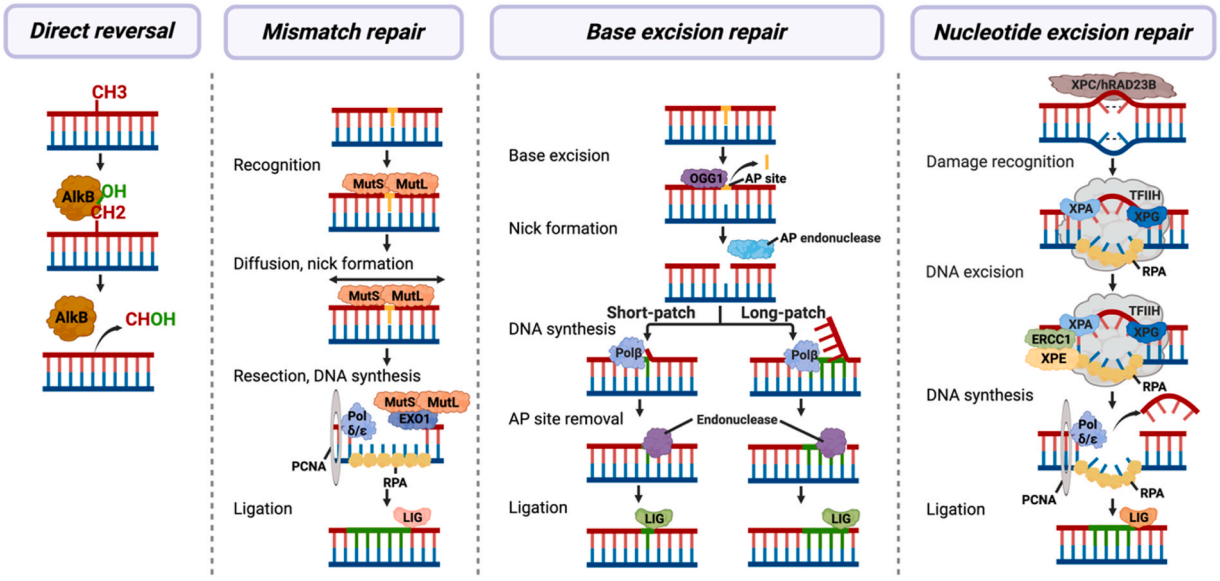

Fig. 1. The schematic diagrams of the direct reversal pathway, MMR, BER, and NER. The direct reversal pathway can directly reverse DNA lesions using single repair proteins, without the need to incise the DNA backbone. In repairing N-alkylated base adducts through the direct reversal pathway, AlkB family dioxygenases catalyze the hydroxylation (addition of -OH) of the methyl group ($-CH_3$) on the damaged DNA base. Subsequently, the hydroxylated methyl group ($-CH_2$-OH) spontaneously dissociates as formaldehyde (-HCOH), thus restoring the normal base. The MMR pathway facilitates the removal of base-base mismatches and insertion-deletion mismatches. MMR begins with the recognition of mismatches by the MutS and MutL heterodimers, followed by the diffusion of these complexes to nick the DNA either upstream or downstream of the mismatch. This DNA nick serves as an entry point for EXO1, which functions to remove a segment of DNA. Subsequently, Pol δ and ε fill the nucleotide gap, and then LIG ligates the 3'-OH and 5'-phosphate groups in the DNA backbone. The BER pathway is responsible for eliminating small base lesions resulting from deamination, oxidation, alkylation, and depurination/depyrimidination. The BER pathway is initiated by distinct damage-specific DNA glycosylases, such as OGG1, which recognize the damaged base, catalyze the cleavage of an N-glycosidic bond, release a free base, and create an AP-site. The AP endonuclease then incises the AP-site for subsequent processing through either short-patch or long-patch BER. In short patch BER, Pol β removes the 5′-deoxyribosephosphate residue generated by AP endonuclease and generates a DNA nick ready for ligation by LIG after endonuclease removing the AP-site. The NER pathway handles a variety of helix-distorting lesions, including bulky DNA adducts and intra-strand crosslinks. Damage recognition in NER occurs through global genome repair or transcription-coupled repair. In global genome repair pathway (as shown here), the entire genome is examined for helix distortions by the XPC complexed with hRAD23B and centrin 2. After initiation, a short oligonucleotide containing the damage is released from the DNA, and then the resulting nucleotide gap is filled by Pol δ or ε for subsequent ligation by LIG. **Abbreviations:** AP: apurinic/apyrimidinic; BER: base excision repair; EXO1: exonuclease 1; LIG: DNA ligase; MMR: mismatch excision repair; NER: nucleotide excision repair; OGG1: 8-oxoguanine DNA glycosylase-1; PCNA: proliferating cell nuclear antigen; Pol β: DNA polymerase β; Pol δ or ε: DNA polymerase δ or ε; RPA: replication protein A.

these damaged bases. The BER pathway is initiated by distinct damage-specific DNA glycosylases, such as 8-oxoguanine DNA glycosylases I (OGG1) and II, neilike DNA glycosylases 1 and 2 (NEIL1 and 2), MTH1 and MUTYH.

These DNA glycosylases recognize the damaged base, catalyze the cleavage of an N-glycosidic bond, release a free base, and leave an apurinic/apyrimidinic site (AP-site) (Krokan and Bjørås, 2013). In the BER pathway, the initiation is then followed by subsequent common steps, including strand incision, end processing, repair synthesis, and ligation of the nick, which are catalyzed by AP-endonuclease, exonuclease, DNA polymerase, and ligase, respectively. Two general BER pathways have been identified: the short-patch BER pathway is responsible for repairing a single nucleotide, while the long-patch pathway repairs at least two nucleotides (Robertson et al., 2009). Additionally, a specialized BER pathway, termed SSB repair (SSBR), is responsible for detecting and repairing SSBs. Poly (ADP ribose) polymerase (PARP) serves as the key enzyme actively involved in SSBR (Fisher et al., 2007). SSBs are rapidly detected and bound by PARP1 (Satoh and Lindahl, 1992), which adds poly (ADP ribose) (PAR) to itself and other target proteins. Subsequently, PARP1 or PARP2 recruits X-ray repair cross-complementing protein 1 (XRCC1) (Schreiber et al., 2002; El-Khamisy et al., 2003), which functions as a scaffold for recruiting other necessary factors. PARP1 may also have other potential roles in SSBR, such as promoting gap-filling and participating in final DNA ligation by facilitating ATP supply (Caldecott, 2008; Oei and Ziegler, 2000). PARP2, while having 18-fold lower activity compared to PARP1, can support up to a quarter of the normal level of PAR synthesis induced by DNA damage in the absence of PARP1 (Amé et al., 1999), suggesting an overlapping or backup role of PARP2 for PARP1 (Fig. 1).

2.4. Nucleotide excision repair (NER)

Unlike BER, which only removes bases, NER excises entire nucleotides. The NER pathway deals with a variety of helix-distorting lesions, including cyclobutane–pyrimidine dimers, bulky DNA adducts, and intra-strand crosslinks, which can interfere with base pairing and impede transcription and replication. The detection of DNA damage in NER is achieved through global genome repair (GGR) or transcription-coupled repair (TCR) (Schärer, 2013).

In the GGR pathway, the entire genome is examined for helix distortions by XPC complexed with hRAD23B and centrin 2, whereas TCR only repairs lesions in the transcribed strand of active genes when RNA polymerase II is stalled during transcript elongation (Marteijn et al., 2014). After the initiation of NER, a short damage-containing oligonucleotide is released from DNA, and the resulting gap is filled in by a transcription initiation complex called TFIIH, which is involved in both GGR and TCR (Cleaver et al., 2009). Previous studies have shown that mutations in NER-related genes can lead to cancer and premature aging disorders (Marteijn et al., 2014) (Fig. 1).

2.5. Double-strand DNA break (DSB) repair

DSBs are considered to be the most cytotoxic DNA lesions, with a single unresolved DSB leading to chromosome rearrangement and consequently compromising cell viability (Ketley and Gullerova, 2020). Two pathways, homologous recombination (HR) and non-homologous end joining (NHEJ) have evolved to repair DSBs (San Filippo et al., 2008; Lieber, 2008).

HR is largely restricted to the S/G2 phases of the cell cycle when DNA is replicated. During HR, the existing sister chromatid is used as a homologous template for DNA repair, enabling high fidelity (San Filippo et al., 2008). In eukaryotic cells, the critical step for the commitment to HR is end resection, which commences with the recruitment of the MRE11–RAD50–NBS1 (MRN) complex to DSB (Symington and Gautier, 2011). NBS1 facilitates the translocation of the MRN complex to the DNA damage site through its nuclear localization signal and its interaction with MRE11 (Desai-Mehta et al., 2001). Integration of the MRN complex with DNA is facilitated by MRE11, and dimerization of MRE11 and RAD50 serves to stabilize the MRN complex while bringing DNA termini into proximity. Additionally, MRE11 possesses both endo- and exonuclease activities directed towards both single-stranded DNA (ssDNA) and double-strand DNA (dsDNA), initiating the DNA resection process (Paull and Gellert, 1998; Williams et al., 2008; de Jager et al., 2001). Ataxia telangiectasia mutated (ATM), one of the DDR kinases primarily activated by DSB, is subsequently recruited through its interaction with NBS1 (Uziel et al., 2003). In normal cells, ATM remains inactive in the form of multi-dimers or homodimers. However, in response to DSBs, it undergoes autophosphorylation and dissociates to form active monomers (Bakkenist and Kastan, 2003). Once stimulated, ATM plays a pivotal role in transmitting and amplifying DDR signals by phosphorylating multiple downstream substrates. Another crucial DDR kinase is ATM and RAD3-related (ATR), whose activation is linked to the stabilization of DNA replication forks and the regulation of SSB repair processes (Zou and Elledge, 2003). Due to the limited nuclease activity of MRN complex for achieving complete DNA resection, several other factors, including breast cancer protein 1 (BRCA1), CtBP-interacting protein (CtIP), exonuclease 1 (EXO1), bloom syndrome protein (BLM), and Dna2, are also required for the efficient short-range and long-range resection to create long 3' ssDNA tails (Limbo et al., 2007; Cannavo and Cejka, 2014; Garcia et al., 2011). The ssDNA tails are then rapidly coated with abundant ssDNA-binding heterotrimeric complex replication protein A (RPA), to avoid initiating other nucleolytic processes which could cleave ssDNA intermediates. If HR is to proceed, breast cancer protein 2 (BRCA2) will replace RPA with RAD51 recombinase on ssDNA (Jensen et al., 2010; Thorslund et al., 2010). Following the generation of presynaptic filament RAD51-bound ssDNA, homologous sequence on sister chromatid will be invaded and a D-loop structure will be formed (Uryga et al., 2016). Finally, the resolution of Holiday junctions results in two identical DNA sequences (Chapman et al., 2012).

NHEJ can occur throughout the cell cycle, including during the G1 phase, when a sister chromatid is not available (Lieber, 2008). Unlike HR, NHEJ can be an error-prone process, that does not use a homologous template and directly ligates the two broken DNA ends together (Chapman et al., 2012). After NHEJ is initiated by Ku70-Ku80 heterodimer binding to the DSB ends, other factors are recruited, including DNA-dependent protein kinase catalytic subunit (DNA-PKcs), DNA ligase IV (LIG4), the associated scaffolding factors X-ray repair cross-complementing protein 4 (XRCC4), XRCC4-like factor (XLF) and the paralogue of XRCC4 and XLF (PAXX) (Ahnesorg et al., 2006; Nick McElhinny et al., 2000; Ochi et al., 2015). In NHEJ, DSB ends are processed by nuclease Artemis, specialized DNA polymerase λ and μ, and other enzymes that ensure the compatibility of the ligated ends (Stinson et al., 2019). The synapsis of the two DSB ends is a two-step process (Blackford and Jackson, 2017): first, long-range synapsis is established by Ku70-Ku80 and DNA-PKcs, followed by closer alignment of the two DSB ends mediated by XLF, XRCC4-LIG4, and DNA-PKcs. Additionally, DSBs can also be repaired through alternative end joining (aEJ), also called microhomology-mediated end joining (MMEJ), which is different from the classical NHEJ pathway. The aEJ pathway is initiated by CtIP-dependent end resection which generates short termini of one to four nucleotides, which are further processed via PARP1, Polθ, dRP lyases, XRC1, LIGI, and LIGIII (Mateos-Gomez et al., 2015) (Fig. 2).

2.6. DNA damage tolerance (DDT)

In eukaryotic cells, some lesions encountered during DNA replication are tolerated and the replication is completed with unrepaired templates. Unlike those DDR pathways that restore the proper sequence and structure of DNA, DNA lesions remain present after DDT. Mammalian cells have developed two types of DDT, namely template switching (TS) (Branzei, 2011) and translesion synthesis (TLS) (Waters et al., 2009). TS is an error-free DDR pathway that relies on the nascent DNA strand

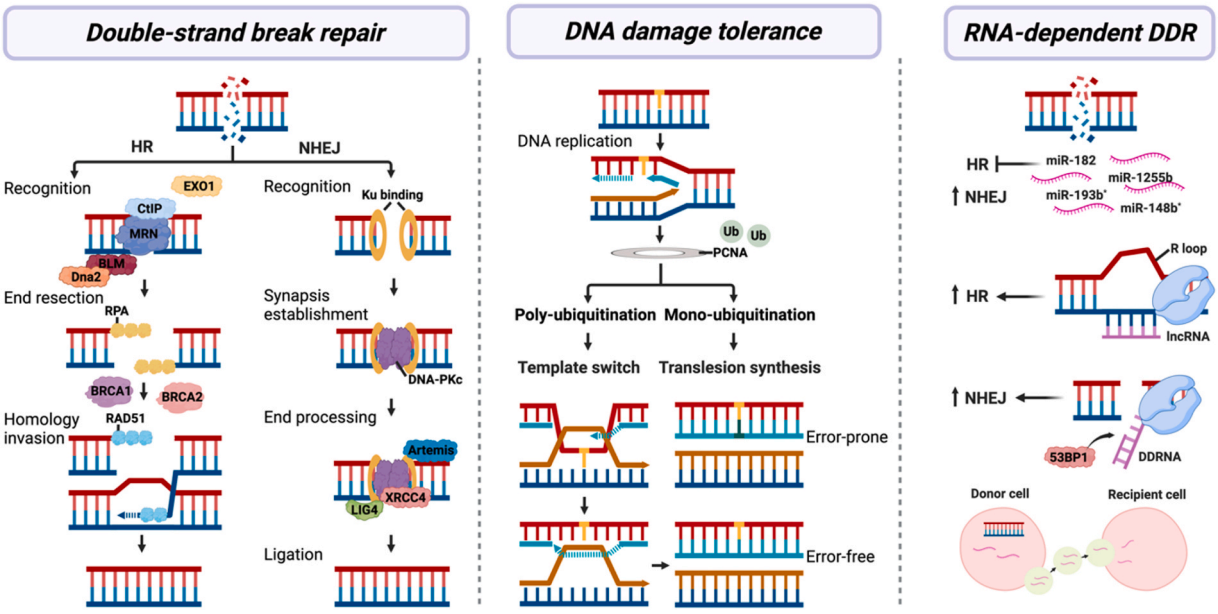

Fig. 2. The schematic diagrams of the DSB repair, DDT, and RNA-dependent DDR. "→" represents promotion; "⊥" represents inhibition. Two pathways, HR and NHEJ, have evolved to repair DSB. The HR pathway initiates with end resection via MRN complex. CtIP, EXO1, BLM, and Dna2 are also necessary to generate 3' ssDNA tails, which are rapidly coated with RPA, followed by RAD51 loading. The RAD51-bound ssDNA tails then search for a homologous sequence on the sister chromatid to invade, ultimately resulting in the generation of two identical DNA sequences. In contrast, the NHEJ pathway commences with the binding of the Ku70-Ku80 heterodimer to the ends of DSBs. Subsequently, the Ku70-Ku80 heterodimer, along with DNA-PKcs, establishes long-range synapsis, followed by the closer alignment of the two DSB ends mediated by XRCC4-LIG4 and DNA-PKcs. Artemis processes the DSB ends during the process. The DDT pathway allows for the completion of DNA replication with unrepaired templates. The status of PCNA plays a pivotal role in choosing between two types of DDT: error-free TS and error-prone TLS. Monoubiquitinated PCNA facilitates TLS, while polyubiquitinated PCNA promotes TS. RNA-dependent DDR has recently gained recognition. For instance, miR-182 miR-1255b, miR-148b*, and miR-193b* have been identified as factors that can impair HR-mediated DSB repair, favoring NHEJ-mediated DSBs repair. Moreover, ncRNAs can regulate DDR pathways through gene expression-independent manners. For example, the DNA: RNA hybrids formed by lncRNAs interacting with complementary DNA strands in HR are crucial intermediates in DSB repair, while DDRNAs facilitate the recruitment of 53BP1 to DSBs, enhancing DDR at the mediator level. Intercellular transfer of ncRNA species through exosomes may also play a significant role in DDR for both donor and recipient cells. **Abbreviations:** BLM: bloom syndrome protein; BRCA1: breast cancer protein 1; BRCA2: breast cancer protein 2; CtIP: CtBP-interacting protein; DDR: DNA damage response; DDRNAs: DNA damage response small RNAs; DDT: DNA damage tolerance; DNA-PKcs: DNA-dependent protein kinase catalytic subunit; DSB: double-strand DNA break; EXO1: exonuclease 1; HR: homologous recombination; LIG4: DNA ligase IV; lncRNA: long non-coding RNA; miR: microRNA; MRN: MRE11–RAD50–NBS1; ncRNA: non-coding RNA; NHEJ: non-homologous end joining; PCNA: proliferating cell nuclear antigen; RPA: replication protein A; ssDNA: single-stranded DNA; TLS: translesion synthesis; TS: template switching; XRCC4: X-ray repair cross-complementing protein 4.

exchange between damaged and intact newly synthesized sister chromatid to reactivate replication (Goodman and Woodgate, 2013; Cipolla et al., 2016). In TLS, low-fidelity and error-prone TLS polymerases (such as Rev1, Polζ, and Polη) that can bypass lesions, replace high-fidelity DNA polymerases. When encountering lesions during DNA replication, the status of proliferating cell nuclear antigen (PCNA) is the key to choosing between TS and TLS. Studies have indicated that mono-ubiquitylated PCNA facilitates interaction with TLS polymerases (Stelter and Ulrich, 2003; Kannouche et al., 2004), while the polyubiquitylated form facilitates error-free DDT via TS (Pfander et al., 2005; Papouli et al., 2005; Zhang and Lawrence, 2005). Apart from the post-translational modifications of PCNA, the chromatin organization is also an important regulator of DDT; for example, the chromatin status, sister chromatid cohesion, and chromosome architectural changes are mediated by DNA bending (Branzei and Psakhye, 2016; Che et al., 2021). Masłowska et al (Masłowska et al., 2019). showed that only a single unrepaired DNA lesion could reduce the survival of a budding yeast cell with deficient DDT, suggesting a critical role of DDT in cell viability (Fig. 2).

2.7. RNA-dependent DDR

The DDR process was previously thought to be solely regulated by proteins, however, the essential roles of non-coding RNA (ncRNA) in DDR pathways have been gradually recognized. The ncRNA species can be grouped into long ncRNA (lncRNA) over 200 nucleotides in length and small ncRNA (sncRNA) with a length of < 200 nucleotides. These ncRNA species can be further processed into microRNAs (miRNAs) and other types of RNAs exhibiting versatility in DDR, especially in the DSB repair pathways of HR and NHEJ (Ketley and Gullerova, 2020). Studies have found that miRNA can post-transcriptionally silence various genes encoding key DDR proteins by targeting their mRNAs (van Kouwenhove et al., 2011). For example, miR-182 can target BRCA1, a core component in the DSB repair pathways of HR. Moskwa et al (Moskwa et al., 2011). have indicated that the overexpression of miR-182 could downregulate the expression of BRCA1 protein, impair the HR-mediated DSBs repair, shift to the NHEJ-mediated DSBs repair, and render cells more hypertensive to irradiation. Other miRNAs, reported downregulating the HR-related factors, including miR-1255b, miR-148b*, and miR-193b*, are capable of controlling the levels of BRCA1, BRCA2, and RAD51, respectively (Choi et al., 2014). Besides, miR-15, miR-34, miR-181/182, miR-199, and miR-217 are shown to be associated with the dysfunction of the PARP/SIRT1 DDR system (Pourrajab et al., 2015). Additionally, ncRNAs can also regulate DDR pathways through gene expression-independent manners, such as controlling the localization of DDR proteins, stabilizing DNA ends for resection, and scaffolding multiple factors to promote DDR (Shaw and Gullerova, 2021). For example, DSB-induced RNAs (diRNAs) and DNA damage response small RNAs (DDRNAs) can facilitate the recruitment of multiple DDR factors (such as MDC1, pATM, BRCA1, and 53BP1) to DSBs, stimulating DDR at the mediator level (Francia et al., 2012; Wei et al., 2012). Additionally, in HR, the DNA: RNA hybrid, formed by lncRNAs interacting with the

complementary DNA strand, is an essential intermediate for DSB repair (Liu et al., 2021). Interestingly, evidence suggests that the intercellular ncRNA species transferred through exosomes might also be important in DDR for both donor and recipient cells (Shaw and Gullerova, 2021). Further insight into the mechanisms of RNA-dependent DDR is warranted (Fig. 2).

3. Characteristics of vascular aging

Vascular aging is a complex and dynamic process that involves multiple factors, such as oxidative stress, chronic inflammation, increased apoptosis, and exacerbated cellular senescence (Ungvari et al., 2020). Moreover, these factors also interact with each other. The combination of these factors mainly affects the arterial media-intima layer, which consists of endothelial cells (ECs) and vascular smooth muscle cells (VSMCs). Previous studies have indicated that the structural damage and dysfunction of ECs and VSMCs are closely related to vascular aging and age-related CVDs (Monk and George, 2015). DNA damage plays an important causal role in the dysfunction of ECs and VSMCs during vascular aging. For example, a high level of chromosomal aneuploidy has been reported in ECs isolated from human aorta, especially from atherosclerotic lesions (Tokunaga et al., 1998). Plaque-derived VSMCs exhibit elevated expression of various DSB and DSB repair-related factors, such as the MRN complex and the phosphorylated form of ATM, compared to normal VSMCs cultured in vitro (Mahmoudi et al., 2008; Gray et al., 2015).

Vascular aging is associated with multiple macroscopic characteristics (Fig. 3). The increase in vascular diameter and the thickening of arterial walls (mainly the intima) are prominent structural changes in large elastic arteries during aging (Lakatta, 1993). Epidemiological studies showed that intima-medial thickness (IMT) of the carotid wall increases 2–3 fold between 20 and 90 years of age (Lakatta and Levy, 2003). DNA damage may play a causal role in these vascular aging-related changes. Previous studies have reported a negative correlation between DNA damage in lymphocyte and total antioxidant capacity (TAC) (Demirbag et al., 2005), as well as between TAC and atherosclerotic thoracic aortic IMT (Demirbag et al., 2006). In a study conducted by Gur et al (Gur et al., 2007)., transesophageal echocardiography was employed to measure the IMT of the thoracic aorta. Their analysis further revealed a direct and positive correlation between lymphocytic DNA damage and aortic IMT in a multiple linear regression analysis.

Chronic inflammation is another important age-related vascular characteristic. Studies have shown that aging is associated with chronic low-grade inflammation, which predisposes the vascular system to atherosclerosis (Franceschi et al., 2000). Nuclear transcription factor kappa B (NF-κB) is a critical factor converging multiple proinflammatory pathways in aged arterial walls. This age-associated induction of NF-κB significantly contributes to the activation of ECs, which is important in initiating the atherogenic process (Csiszar et al., 2008a). C-reactive protein (CRP) and adiponectin are also inflammatory markers that participate actively in vascular damage and target-organ lesions. Adiponectin, a plasma protein derived from adipocytes, acts as an anti-atherogenic endogenous factor. Tsioufis et al (Tsioufis et al., 2007). showed that high CRP levels and low adiponectin levels exert an additive detrimental effect on aortic stiffness and accelerate the vascular aging process.

Vascular calcification is a process that reduces the elasticity of the arterial wall as people age. Previous clinical studies have reported that more than 90% of men and 67% of women $\geq$ 70 years old have arterial calcification (Liu et al., 2015). During vascular calcification, VSMCs change into osteoblast-like phenotype and express osteogenic markers (Benetos et al., 2011; Ganesh et al., 2001). Perivascular stem/progenitor cells (pericytes) and ECs can transform into osteoblasts and chondrocytes and contribute to vascular calcification (Boström et al., 1993; Medici et al., 2010). Furthermore, DNA damage may also play an important role in this process. Antibody staining for oxidative DNA damage markers shows that VSMCs at the site of calcification have DNA damage (Müller et al., 2019). Additionally, persistent DNA damage is also found in VSMCs cultured from children on dialysis who rapidly develop medial vascular calcification (Sanchis et al., 2019).

Arterial stiffening is also a hallmark of vascular aging and has been identified as an independent predictor of future cardiovascular events (Durham et al., 2018). Histological examination shows that the aged arterial blood vessels are associated with multiple structural alterations, including excessive collagen, reduced elastin, elastin fractures, and

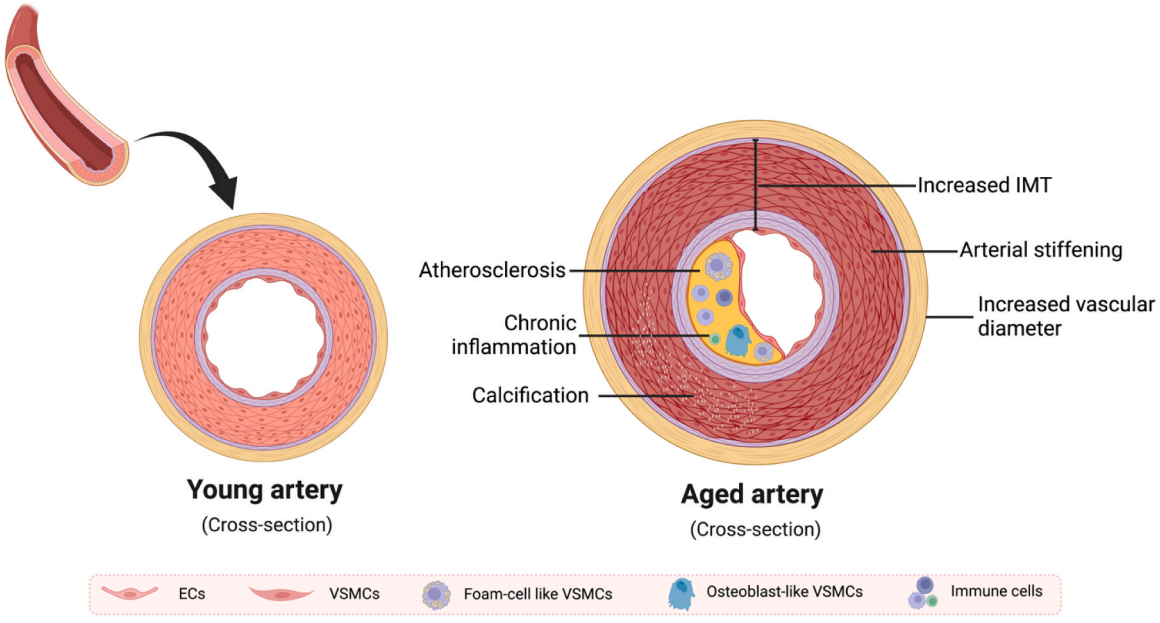

Fig. 3. Macroscopic characteristics of vascular aging. Aged arteries exhibit a range of features, such as increased vascular diameter and IMT, chronic inflammation, vascular calcification, arterial stiffening, and the development of atherosclerosis. Within the context of atherosclerosis, lipid deposition between the intimal and medial layers of the blood vessel can induce chronic inflammation, immune cell infiltration, and the differentiation of VSMCs into foam-cell-like and osteoblast-like VSMCs. **Abbreviations:** ECs: endothelial cells; IMT: intima-medial thickness; VSMCs: vascular smooth muscle cells.

calcification of the vascular media, as well as luminal dilation and intimal thickening (Lakatta and Levy, 2003). All these histological changes contribute to the reduction of arterial compliance and the capacity of arteries to resist stress (Benetos et al., 2011). Pulse wave velocity (PWV) has long been regarded as the gold standard evaluation of arterial stiffness. Previous studies reported that young individuals have more elastic arteries, while PWV significantly increases in older individuals (Mikael et al., 2017). Arterial stiffening may provoke systolic hypertension, poor cardiac perfusion, and eventually cardiac remodeling and heart failure (Lanzer et al., 2014). Considering its important role in the development of age-related CVDs, the assessment of arterial stiffness has long been recommended to improve the risk stratification of cardiovascular events (Laurent et al., 2006; Mancia et al., 2013).

Atherosclerosis is an age-related disease with complex vascular alterations that can also be observed in aging individuals (Ferrari et al., 2003). Vascular cell senescence has been shown to play a pivotal role in the atherogenic process (Minamino and Komuro, 2007). Since vascular aging and atherosclerosis are associated with similar biochemical pathways and vascular alterations, atherosclerosis might be regarded as a specialized form of accelerated vascular aging. Abundant evidence suggests that DNA damage in vascular cells possibly acts as a crucial mediator in vascular aging and atherosclerosis (Gray et al., 2015; Mercer et al., 2010; Martinet et al., 2002). Both “macro” and “micro” DNA damage has been found in the human atherosclerotic plaque: “macro” damage includes deletions or additions of parts or whole chromosomes, while “micro” damage includes DNA modifications or adducts, DSBs, loss of heterozygosity (LOH) and MSI (Mahmoudi et al., 2006).

4. DDR in vascular aging, a double-edged sword

4.1. Deficient DDR in vascular aging

DDR is a complex and conserved signaling cascade that involves networks of interacting processes, such as cell cycle checkpoints, transient senescence, and apoptotic pathways (Andreassi, 2008). A study that combined genetic risk factors associated with the comorbidity of CVDs showed significant enrichment of DDR-related genes (Turk and Kunej, 2022), suggesting an important role of DDR in vascular aging. Considering the important role of DNA damage in age-related vascular diseases, one might speculate that deficient DDR, which could result in the accumulation of unrepaired damaged DNA, can also lead to vascular aging.

Premature aging syndromes with DDR defects and characterized by age-related clinical phenotypes, support this hypothesis. Hutchison-Gilford progeria syndrome (HGPS) is caused by a mutation in the *LMNA* gene encoding lamin A (Eriksson et al., 2003), of which the premature accumulation has been demonstrated to be toxic to DDR (Cobb et al., 2016). HGPS children suffer from exacerbated CVDs, including premature arteriosclerosis, calcification, vascular stiffening, and coronary artery and cerebrovascular diseases; and they typically die of myocardial infarction (MI) or stroke at an average of 14.6 years (Gordon et al., 2014). Another premature aging syndrome characterized by vascular aging-related CVDs is Werner syndrome, caused by loss-of-function mutations in genes encoding Werner syndrome ATP-dependent helicase (WRN). All model organisms of the Werner syndrome are hypersensitive to DNA damage, supporting the hypothesis of WRN being a DDR protein (Opresko, 2008). Patients with Werner syndrome exhibit premature cardiovascular features such as atherosclerosis and usually die from MI due to accelerated atherosclerosis at a mean age of 54 years (Epstein et al., 1966). Zhang et al (Zhang et al., 2015). found that the level of WRN protein in healthy individuals also varies with age. They found that the WRN protein level in primary wild-type mesenchymal stem cells (MSCs) obtained from elderly healthy individuals is significantly lower than those from young individuals. These findings suggest that an age-dependent decrease in WRN expression in MSCs may lead to an increased number of dysfunctional MSCs in normal older individuals. Therefore, WRN might be a novel therapeutic target for treating age-related CVDs observed in the general population.

Ineffective MMR has been largely reported in malignancies (Bonadona et al., 2011), while evidence of its effect on age-related diseases is relatively limited. Recently, Perry et al (Perry et al., 2014). reported an association between polymorphisms of MMR gene *MSH6*, especially variant rs1800932, and the age at menopause. Evidence has shown that LOH and MSI, which may be the indicators of MMR deficiency, were involved in the development of atherosclerotic plaques (Hatzistamou et al., 1996). Flouris et al (Flouris et al., 2000). detected the presence of LOH in hMSH2, hPMS1, and hMLH1 in human autopsy cases of atherosclerosis. This finding might suggest that such genomic alterations are important events in the atherogenic process. Microsatellite analysis also reveals a significant incidence of LOH and MSI in specific loci on chromosomes 2, 8, 9, and 17 on cerebral atherosclerotic plaques (Miniati et al., 2001).

Evidence from animal studies shows that alterations in NER-related components may also be causative in vascular aging. Two NER-defect mouse models, XPD^{TTD} mice with moderately accelerated aging and $Ercc1^{d/-}$ mice with much faster aging paces, have been developed to evaluate the role of NER on aging (de Boer et al., 1998; Dollé et al., 2006). Both XPD^{TTD} and $Ercc1^{d/-}$ mice are associated with increased vascular cell senescence, accelerated vasodilator dysfunction, increased vascular stiffness, and elevated blood pressure at a very young age (Durik et al., 2012). Additionally, the finding that the $Ercc1^{d/-}$ mice develop more accelerated endothelial dysfunction than the XPD^{TTD} mice is consistent with the relative pace of aging acceleration of these two strains. They also found that arterial stiffness is associated with the single-nucleotide polymorphisms (SNPs) of human NER component genes, especially rs2029298 SNP of genes encoding the DNA damage-recognition complex XPE. Previous studies indicated that the polymorphisms in the NER-related genes XPD and ERCC5 (Asp1104His) are associated with genomic instability in coronary diseases and the risk of atherosclerosis and stroke (Shyu et al., 2012; Bazo et al., 2011). Chinese Han populations with the *ERCC1* gene rs11615 SNP show susceptibility to coronary artery diseases and the severity of coronary atherosclerosis (Zhang et al., 2017). All these findings suggest an important role of NER deficiency in vascular aging.

BER is a highly conserved DDR pathway responsible for repair of small base lesions. OGG1 is a key regulatory BER enzyme responsible for repairing 8oxo-dG lesions, of which extensive accumulation is found in ECs, VSMCs, and macrophages in the advanced atherosclerotic plaques (Martinet et al., 2002). The reduced activity of OGG1 leads to the defective repair of nuclear 8oxo-dG in human plaques; additionally, the level of 8oxo-dG in vivo and atherosclerosis increases in $OGG1^{-/-}$ mice, while rescuing the activity of OGG1 can reduce the accumulation of 8oxo-dG and the development of atherosclerotic plaques (Shah et al., 2018). Tumurkhuu et al (Tumurkhuu et al., 2016). indicated that *OGG1* knockout in macrophages promotes the atherogenic process; they also found a reduced expression of OGG1 transcript in human plaques compared with normal vessels. NEIL3 is an important DNA glycosylase involved in the BER pathway. Compared to $ApoE^{-/-}$ mice, $NEIL^{-/-}$apolipoprotein E $(ApoE)^{-/-}$ mice show accelerated plaque formation on a high-fat diet (Skarpengland et al., 2016); this might be explained by the role of NEIL3 in balancing lipid metabolism and macrophage function in the development of atherosclerosis. NEIL3 deficiency can also promote atherogenesis through noncanonical mechanisms affecting the VSMC phenotype, for example, by activating the Akt signaling pathway (Quiles-Jiménez et al., 2021). Except for these aforementioned cellular, histological, or animal studies, genetic studies also showed that polymorphisms in BER-related genes may partially explain the different risks of developing age-related vascular dysfunctions. For example, the rs12645561 SNP TT genotype of NEIL3 is associated with an increased risk of MI (Skarpengland et al., 2015). Polymorphisms in the *BER* genes encoding XRCC1 and XPD are associated with a higher risk for coronary atherosclerosis (Bazo et al., 2011; Guven et al., 2007). The rs25487

polymorphism of the *XRCC1* gene represents a significantly reduced risk of ischemic stroke (He et al., 2016; Mahabir et al., 2007). XRCC1 Arg399Gln and OGG1 Ser326Cys gene polymorphisms are also biomarkers for the risk of ischemic stroke (Orhan et al., 2016). Furthermore, the ERCC2 Lys751Gln variant is associated with the risk of large artery atherosclerotic stroke, especially in smokers (Shyu et al., 2012).

DSBs are reported to be the most lethal DNA lesions in the cell, and defective repair of DSB might also play an important role in vascular aging-related diseases. Gray et al (Gray et al., 2015). showed the expression of multiple DDR proteins, particularly the MRN complex that senses DSBs, is increased in human atherosclerotic plaques. Although the extent and composition of atherosclerotic plaques are not influenced by accelerating or hindering the DSB repair, faster DSB repair reduces the vulnerability of plaques by increasing the relative fibrous cap area and the VSMC content. Data from genome-wide association studies (GWAS) showed that DSB repair pathways, especially the rs2155209 polymorphism of the *MRE11A* gene encoding a subunit of DSB sensor MRN, are associated with the occurrence of MI (Verschuren et al., 2013). The rs2155209 polymorphism of the *MRE11A* gene is also associated with lower severity of subclinical atherosclerosis, while the rs13447720 and rs499952 variants are associated with a decreased risk (Vargas-Alarcón et al., 2019). RAD52 is another protein that carries out important functions in the repair of DSBs (Bhowmick et al., 2016). In patients with ischemic heart diseases, the rs7963551 G/T heterozygotes of RAD52 exhibit significantly increased mortality compared with the GG or TT homozygotes (Lenart et al., 2017). This finding suggests that SNPs affecting the efficiency of DSB repair may influence vascular aging in humans.

The important regulatory roles of miRNAs in DDR have gradually been illuminated. For example, miR-16, miR-31, and miR-17–3p can regulate vascular inflammation by influencing the expression of adhesion molecules, such as vascular cell adhesion molecule 1 (VCAM-1), intercellular cell adhesion molecule-1 (ICAM-1), and E-selectin (Suárez et al., 2010; Asgeirsdóttir et al., 2012). Ito et al (Ito et al., 2010). and Menghini et al (Menghini et al., 2009). demonstrated that miR-217 and miR-34a can induce human ECs senescence by targeting the SIRT pathway. Besides, miR-155 and miR-125–5p are found to be associated with the stability of lipid uptake, monocyte/macrophage inflammation, and neointimal foam cell accumulation, thereby influencing the development of atherosclerotic plaque (Chen et al., 2009; Nazari-Jahantigh et al., 2012). LncRNA *SNHG12* can bind to DNA-PKs and enhance the ability of DDR by facilitating the binding of DNA-PKs to Ku70/80 in vascular ECs (Haemmig et al., 2020). The knockdown of *SNHG12* can increase DNA damage and cellular senescence both in vitro and in vivo, thereby exacerbating the EC dysfunction and macrophage efferocytosis. Considering their important roles in modulating cardiovascular signal transduction, miRNAs might be novel therapeutic targets in treating age-related CVDs. Lovren et al (Lovren et al., 2012). showed that the overexpression of miR-145 in VSMCs can improve the stability of atherosclerotic plaques by increasing the fibrous cap area and plaque collagen content while reducing the necrotic core area.

Except for the aforementioned key components of DDR, DDR signaling proteins also play pivotal roles in vascular aging. In cells, DNA lesions first activate various kinases, such as ATM and ATR, which act as the primary transducers in the DDR signaling cascade. Thrasher et al (Thrasher et al., 2017). noticed that ATM variants may predispose individuals to ischemic heart diseases. $ATM^{+/-}$ VSMCs and macrophages exhibit increased nuclear DNA damage, as well as defective DDR signaling, growth arrest, and apoptosis, which further promote the development of atherosclerosis and metabolic syndrome (Mercer et al., 2010). Similarly, Wu et al (Wu et al., 2005). showed that $ATM^{+/-}ApoE^{-/-}$ mice are associated with significantly higher plasma cholesterol levels and more advanced aortic atherosclerotic lesions compared with $ATM^{+/+}ApoE^{-/-}$ mice. Sirtuin is another important class of DDR signaling proteins. Once activated, sirtuins can significantly increase the ATM expression and phosphorylate MRE11 and NBS1, thereby promoting the formation of the MRN complex and increasing the activation of DDR (Bartoli-Leonard et al., 2021). A previous study found that the impairment of SIRT1-mediated DDR is involved in the bisphenol A-induced aggravation of macrophage inflammation and atherosclerosis (Yang et al., 2021). Bartoli-Leonard et al (Bartoli-Leonard et al., 2021). reported that SIRT loss accelerates while its activation attenuates the DNA damage-induced vascular calcifications in diabetic patients. A further study discovered that the association between SIRT1 loss and increased calcification might be mediated by the osteogenic transcription factor pathway Runx2 (Bartoli-Leonard et al., 2019; Badi et al., 2018). While the loss of SIRT1 may facilitate vascular aging, heart-specific overexpression of SIRT1 is found to impede heart aging and protect the heart from paraquat-induced oxidative stress (Alcendor et al., 2007). Zhang et al (Zhang et al., 2008). discovered that endothelium-specific overexpression of SIRT1 can suppress atherogenesis in $ApoE^{-/-}$ mice. SIRT6 is also an important DNA damage sensor in the DDR pathways (Mao et al., 2011). SIRT6 is involved in the inflammatory pathways of diabetic atherosclerotic lesions (Balestrieri et al., 2015). Grootaert et al (Grootaert et al., 2021). reported that the expression level of SIRT6 in VSMCs located in human and mouse atherosclerotic plaques is markedly reduced; additionally, the VSMC-specific overexpression of SIRT6 can inhibit atherogenesis and reduce tissue markers of cell senescence and inflammation. SIRT6 can also prevent the degradation of hepatic low-density lipoprotein (LDL) receptors and lower the level of plasma LDL-cholesterol in mice (Tao et al., 2013), which may impede the atherogenic process.

4.2. Overexpressed DDR in vascular aging

Considering the possible causative role of deficient DDR in vascular aging, several attempts have been carried out to enhance the efficiency of DDR by overexpressing related enzymes to enhance resistance to genomic lesions and retard the aging process. However, a non-physiological level of certain DDR proteins may not be beneficial, or even detrimental to protection from vascular aging.

PARP1 is an enzyme activated by DSBs and physiologically participates in DDR. Moderate activation of PARP1 can facilitate DDR and rescue organs from pathological dying (Csiszar et al., 2005), while excessive activation of PARP1 depletes beta-nicotinamide adenine dinucleotide (NAD^+) and ATP. These depletions further lead to necrotic cell death and the necrotic core formation of atherosclerotic lesions (Carson et al., 1986). Martinet et al (Martinet et al., 2002). identified that human atherosclerotic plaques are associated with an elevated level of PARP1. Additionally, PARP1 signaling can promote the trans-differentiation of VSMCs from a contractile phenotype to the osteogenic phenotype, which enhances the expression of mineralization-regulating proteins, exacerbating calcium deposition (Müller et al., 2019; Wang et al., 2019). These findings might help to explain why PARPs are activated at sites of calcification in animal models and human vessels (Chow et al., 2014). PARP1 over-activation has also been found in endothelial dysfunction, hypertension, diabetes, atherosclerosis, and heart failure (Pacher and Szabó, 2007; Krishnakumar and Kraus, 2010; Wang et al., 2018). Taken together, these results imply a negative role of PARP1 activation in the pathogenesis of age-related CVDs. Actually, studies do observe a protective therapeutic effect of PARP inhibitors. Benkö et al (Benkö et al., 2004). found that INO-1001, a novel potent PARP inhibitor, can improve the endothelial function in ApoE-deficient atherosclerotic mice models on a high-fat diet. Additionally, the inhibition of PARP1/2 can inhibit calcification in rat, bovine, and human targets (Müller et al., 2019). In ST-elevated MI patients undergoing urgent revascularization, PARP1 inhibition using INO-1001 can reduce the level of inflammatory markers and achieve satisfying safety (Morrow et al., 2009). Xu et al (Xu et al., 2014). showed that reducing PARP1 activity by pharmacological or molecular approaches can attenuate the development of atherosclerotic plaques, enhance plaque stability, and promote the regression of

pre-established plaques.

Although haploinsufficiency in ATM is associated with an increased risk of atherosclerosis, ATM inhibition is protective. Its inhibition can reduce both the mRNA and the secreted level of pro-calcific factors in VSMCs, thereby reducing osteogenic differentiation and calcification (Liu et al., 2013). Sanchis et al (Sanchis et al., 2019). also showed that the blockade of ATM-mediated DNA damage signaling can reduce inflammation and vascular calcification in children on dialysis. Caffeine, which can markedly reduce atherogenesis, has recently been found to be an effective DDR inhibitor by inhibiting ATM in VSMCs both in vitro and in vivo (Mercer et al., 2012). These findings might indirectly suggest a biphasic property of ATM in vascular aging.

The overexpression of other DDR enzymes, such as the DNA polymerase β (DNA pol β) and alkyl N-purine glycosylase (ANPG), are also detrimental. DNA pol β is the most inaccurate DNA polymerase in mammalian cells. The overexpression of DNA pol β in human cells increases the risk of spontaneous mutagenesis and the tolerance to bifunctional DNA cross-linking anticancer drugs (Canitrot et al., 1999a, 1999b). Similarly, Chinese hamster ovary (CHO) cells with overexpressed ANPG genes are more sensitive to alkylating agents (Calléja et al., 1999; Coquerelle et al., 1995). However, no studies have investigated the effects of DNA pol β and ANPG in vascular aging, and further studies are warranted.

A brief summary of the role of these overexpressed DDR in vascular aging is shown in Fig. 4.

4.3. Therapies having an effect on DDR in vascular aging

Statins, the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are widely prescribed to atherosclerotic patients to reduce their serum cholesterol. Recently, statins have also been found to have an effect of reducing DNA damage (Shin et al., 2005; Harangi et al., 2004). In end-stage renal disease patients with carotid artery atherosclerosis, simvastatin significantly reduces the chromosomal damage in their lymphocytes (Pernice et al., 2006). However, whether this effect is realized through preventing genomic damage or potentiating the DDR capacity remains unclear. Ostrau et al (Ostrau et al., 2009). showed that the irradiation-induced phosphorylation of histone H2AX (γ-H2AX), an indicator of DSBs, is not affected by lovastatin treatment. They also found that compared with non-treated cells, the number of γ-H2AX foci is identical after 4 h radiation, while significantly reduced after 30 min radiation in lovastatin-pretreated cells. Based on all these findings, these authors speculated that lovastatin might accelerate the radiation-induced DSB repair in vitro, but not affect the residual level of damage. Mahmoudi et al (Mahmoudi et al., 2008). found that atorvastatin can accelerate DDR in human VSMCs via Hdm2 phosphorylation, NBS-1 stabilization, and more rapid phosphorylation of ATM and γ-H2AX. However, Nübel et al (Nübel et al., 2006). found no influence of lovastatin on the ionizing radiation-induced formation and repair of DSBs. Whether statins affect the DDR pathway and the underlying mechanisms requires further investigation.

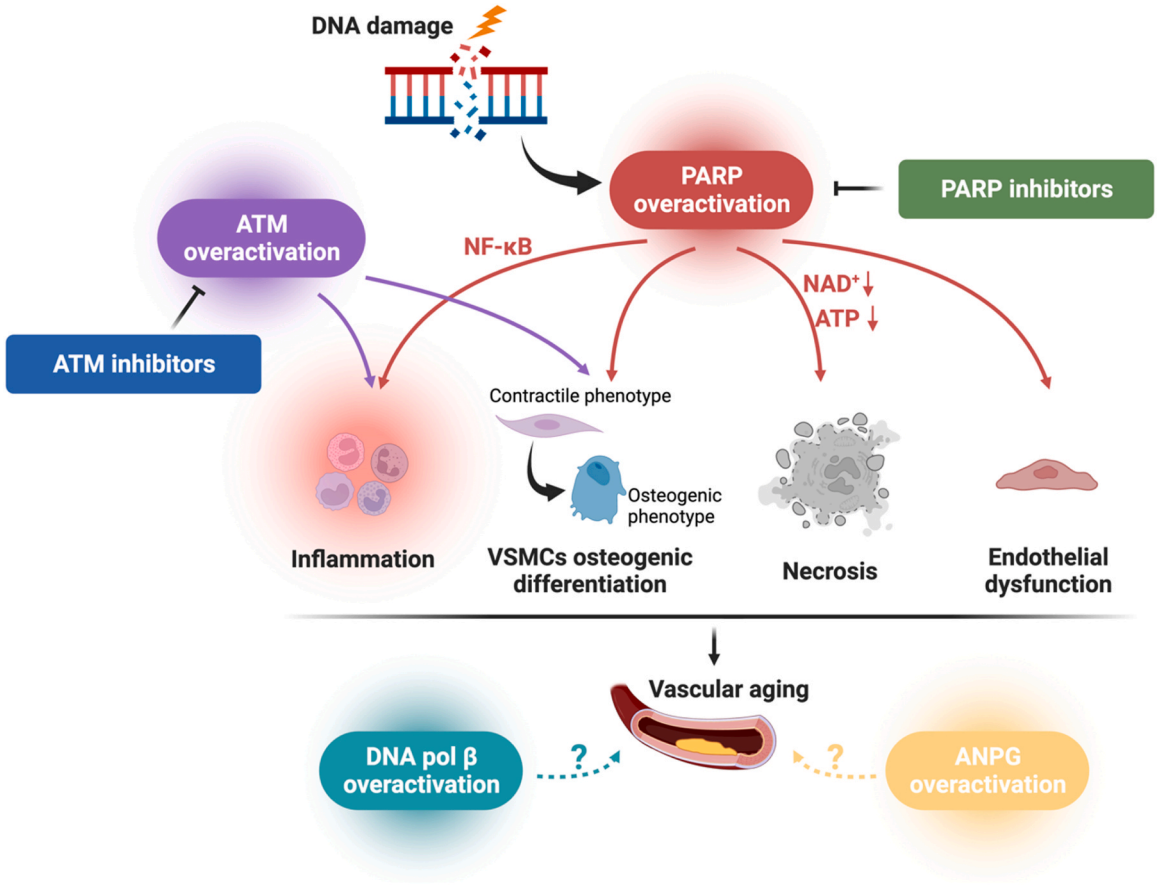

Fig. 4. The role of overexpressed DDR in vascular aging. "⊥" represents inhibition. The overactivation of PARP and ATM, which are physiological participants in DDR, can exacerbate the process of vascular aging, while their inhibitions are protective. Excessive activation of PARP can deplete NAD^+ and ATP, leading to necrotic cell death. Additionally, PARP signaling can promote the trans-differentiation of VSMCs from a contractile phenotype to the osteogenic phenotype. Over-activation of PARP1 has also been observed in endothelial dysfunction, and its inhibition can reduce the levels of inflammatory markers. Inhibition of ATM can reduce inflammation and mitigate the osteogenic differentiation of VSMCs. The effects of overactivation of DNA pol β and ANPG are also detrimental, but their effects in vascular aging require further exploration. **Abbreviations:** ATP: adenosine triphosphate; ANPG: Alkyl N-purine glycosylase; ATM: ataxia telangiectasia mutated; DNA pol β: DNA polymerase β; NAD: nicotinamide adenine dinucleotide; NF-κB: nuclear transcription factor kappa B; PARP: poly (ADP ribose) polymerase; VSMCs: vascular smooth muscle cells.

As we summarized above, SIRT proteins are protective against vascular aging and age-related CVDs in both rodents and humans. This might suggest SIRT1 activators, such as resveratrol, could act as potential therapeutic agents. Csiszar et al (Csiszar et al., 2008b). showed that resveratrol can protect aortic ECs against cigarette-induced apoptotic cell death and attenuate the smoke extract-induced DNA damage in coronary arterial ECs of rats. Resveratrol can also generate anti-atherogenic effects by increasing vascular oxidative stress resistance (Ungvari et al., 2007). Another SIRT1 activator, SRT1720, can ameliorate age-related vascular endothelial dysfunction in mice by enhancing COX-2 signaling and reducing oxidative stress and inflammation (Gano et al., 2014). SRT1720 can also generate athero-protective effects in the angiotensin II-induced atherosclerotic model, characterized by the suppression of inflammatory factors and atherogenic gene expression in the artery (Chen et al., 2015). Except for these animal studies, the effect of SIRT modulators has been evaluated in human studies. In healthy cigarette smokers, oral SIRT1 activator SRT2104 can improve lipid profile by reducing the serum total cholesterol, low-density lipoprotein cholesterol, and triglyceride (Venkatasubramanian et al., 2013) (summarized in Table 1).

5. Future perspectives and conclusions

DNA damage and the subsequent DDR pathways are crucial factors that cause vascular aging. DDR pathways have both positive and negative effects on vascular aging. While some DDR proteins protect against

Table 1
Potential therapies having effects on DDR in vascular aging.

Author (Ref)	Subjects	Intervention	Outcome
Statins			
Mahmoudi et al (Mahmoudi et al., 2008).	t-BHP pre-treated human VSMCs	Atorvastatin	**Statins treatment:** - does not reduce DNA damage (at 1 h); - accelerates DNA repair (from over 6–4 h); - via Hdm2 phosphorylation, NBS-1 stabilization, and more rapid phosphorylation of ATM and γ-H2AX.
Shin et al (Shin et al., 2005).	Hypercholesterolemic patients	Simvastatin 20–40 mg /day for 8 weeks	**Statins treatment:** - significantly reduces DNA damage, as expressed by tail DNA, tail length and tail moment on DNA in lymphocytes.
Harangi et al (Harangi et al., 2004).	Type-II/a hyperlipidemic patients	Atorvastatin 10 mg/ day for 6 months	**Statins treatment:** - significantly decreases DNA damage in comet assay.
Pernice et al (Pernice et al., 2006).	Atherosclerotic patients on maintenance regular acetate-free biofiltration	Simvastatin	**Statins treatment:** - reduces sister chromatid exchanges level and high frequency cells percentages in a dose-dependent fashion.
Ostrau et al (Ostrau et al., 2009).	Irradiated Balb/c mice	Lovastatin	**Statins treatment:** - attenuates ionizing radiation-induced pro-inflammatory and pro-fibrotic responses and cell death in a tissue- and time-dependent manner; - does not affect the γ-H2AX phosphorylation stimulated by ionizing radiation, indicating that statin has no major impact on the induction of DNA damage in vivo.
Nübel et al (Nübel et al., 2006).	Primary human umbilical vein endothelial cells	Lovastatin	**Statins treatment:** - does not influence the formation and repair of ionizing radiation-induced DSB.
SIRT1 activators			
Csiszar et al (Csiszar et al., 2008b).	Male Wistar rats with cigarette smoke exposure	Resveratrol	**SIRT1 activators:** - attenuate the production of reactive oxygen species in rat arteries and cultured coronary arterial endothelial cells; - abrogate the smoking-induced upregulation of inflammatory markers in rat arteries; - protect aortic endothelial cells against cigarette smoking-induced apoptotic cell death; - attenuate cigarette smoke extract-induced DNA damage in cultured coronary arterial endothelial cells (comet assay).
Ungvari et al (Ungvari et al., 2007).	Primary rat coronary arterial endothelial cells	Resveratrol	**SIRT1 activators:** - increase vascular oxidative stress resistance by preventing oxidative stress-induced apoptotic cell death and decreasing H_2O_2 levels; - protect endothelial cells against ultraviolet-induced DNA damage (comet assay).
Gano et al (Gano et al., 2014).	Male B6D2F1 mice	SRT1720	**SIRT1 activators:** - normalize NF-κB activation and reduced TNF-α in old animals; - ameliorate vascular endothelial dysfunction with aging in mice by enhancing COX-2 signaling and reducing oxidative stress and inflammation.
Chen et al (Chen et al., 2015).	Male apoE$^{-/-}$ mice	SRT1720	**SIRT1 activators:** - inhibit atherosclerosis formation and macrophage recruitment induced by AngII; - improve physiological and metabolism parameters after AngII treatment; - attenuate the expression of VSMCs proatherogenic genes; - inhibit inflammatory signaling pathways in vivo and vitro.
Venkatasubramanian et al (Venkatasubramanian et al., 2013).	Healthy cigarette smokers	SRT2104	**SIRT1 activators:** - improve the serum lipid profile, with reductions in concentrations of serum total cholesterol, low-density lipoprotein cholesterol, and triglyceride.

Abbreviations: ATM: ataxia telangiectasia mutated; DSB: double-strand DNA break; NF-κB: nuclear transcription factor kappa B; t-BHP: tert-butyl hydroperoxide; VSMCs: vascular smooth muscle cells.

the onset and progression of aging-related CVDs, others (e.g. PARP1) can be detrimental and may even accelerate the process of vascular aging. This review summarizes the evidence that modulating corresponding DDR pathways pharmacologically or molecularly could have potential therapeutic benefits in managing age-related CVDs. Moreover, miRNA play an important role in vascular aging and understanding their regulation could help prevent and treat age-related vascular diseases in the future. However, the role of DDR in vascular aging remains poorly understood and requires more exploration. Further insights into the basic biology of DDR are required to identify potential therapeutic targets to counteract vascular aging.

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Declaration of Competing Interest

The authors declare no conflict of interest.

Data Availability

No data was used for the research described in the article.

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