There is increasing evidence that human atherosclerosis is associated with damage to the DNA of both circulating cells, and cells of the vessel wall. Reactive oxygen species are the most likely agents inducing DNA damage in atherosclerosis. DNA damage produces a variety of responses, including cell senescence, apoptosis and DNA repair. This review summarises the evidence for DNA damage in atherosclerosis, the cellular responses to damage and the mechanisms of signalling DNA damage.

1. Introduction

Atherosclerotic plaques consist of an accumulation of vascular smooth muscle cells (VSMCs) (for full list of abbreviations, see Table 1) and inflammatory cells, together with lipid and extracellular matrix proteins—advanced plaques also show calcification. Although the plaque develops as a chronic inflammatory reaction, there is increasing evidence that DNA damage to cells within the lesion plays an important role in both atherogenesis and the behaviour of established lesions. DNA damage ranges from ‘macro’ damage, including deletions or additions of whole chromosomes or parts of chromosomes, to ‘micro’ damage, which includes DNA strand breaks, mutations of single bases, modified bases (including oxidation) or DNA adducts. This review outlines the evidence for DNA damage in atherosclerosis, the inducers of damage, the response to damage and repair pathways, the consequences of damage and potential therapies to prevent/reduce damage.

1.1. Evidence for DNA damage in atherosclerosis

DNA damage is present both in the circulation of patients with atherosclerosis and the plaques themselves. For example, patients with coronary artery disease have a higher micronucleus index (a marker of genetic instability) than healthy controls, which correlates with disease severity [1,2]. There is also a significantly higher incidence and extent of a common mitochondrial DNA deletion (mtDNA4977) [3]. Premature atherosclerosis is a feature of defects in DNA repair pathways, such as Werner syndrome, a disease characterised by predisposition to cancer and early onset of symptoms related to normal aging including osteoporosis, ocular cataracts, graying and loss of hair, diabetes mellitus, and atherosclerosis. Werner protein guards the genetic stability of cells, playing an integral role in base excision repair and at telomere ends [4].

There is also evidence of ‘macro’ DNA damage within atherosclerotic plaques. Cytogenetic analysis of primary cell cultures from human plaques identified loss of the Y chromosome and del13q14, XXY karyotype, and trisomy 7, 10 and 18 [5], whilst unstable carotid plaques demonstrated trisomy and tetrasomy of chromosome 7, and monosomy of chromosome 11 [6]. Although it was not clear from these studies which cells had chromosomal...
Table 1
List of abbreviations used

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>8-Oxo-G</td>
<td>8-Oxo-guanine, an oxidative modification of guanine in DNA</td>
</tr>
<tr>
<td>9-1-1</td>
<td>Multiprotein complex consisting of Rad9–Rad1–Hus1</td>
</tr>
<tr>
<td>A–T</td>
<td>Ataxia–telangiectasia</td>
</tr>
<tr>
<td>ATM</td>
<td>Ataxia–telangiectasia mutated (protein)</td>
</tr>
<tr>
<td>ATR</td>
<td>ATM and Rad3-related (protein)</td>
</tr>
<tr>
<td>Chk-1</td>
<td>Checkpoint kinase 1</td>
</tr>
<tr>
<td>Chk-2</td>
<td>Checkpoint kinase 2</td>
</tr>
<tr>
<td>DSBs</td>
<td>Double-stranded (DNA) breaks</td>
</tr>
<tr>
<td>γ-H2AX</td>
<td>Phosphorylated form of the histone protein H2AX</td>
</tr>
<tr>
<td>HMGCoA</td>
<td>3-Hydroxy-3-methylglutaryl coenzyme A</td>
</tr>
<tr>
<td>MDM2</td>
<td>Murine double minute 2 gene</td>
</tr>
<tr>
<td>MRN</td>
<td>Multiprotein complex consisting of MRE11–RAD50–NBS1</td>
</tr>
<tr>
<td>NBS1</td>
<td>Protein mutated in Nijmegen breakage syndrome</td>
</tr>
<tr>
<td>PIKK</td>
<td>Phosphatidylinositol 3-kinase</td>
</tr>
<tr>
<td>ROS</td>
<td>Reactive oxygen species</td>
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<tr>
<td>SIPS</td>
<td>Stress-induced premature senescence</td>
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<tr>
<td>SSBs</td>
<td>Single-stranded (DNA) breaks</td>
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<tr>
<td>VSMC</td>
<td>Vascular smooth muscle cell</td>
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Defects, VSMCs demonstrate microsatellite instability (mutations in microsatellite regions that may affect gene expression) [7,8] and loss of heterozygosity [8], suggesting that genomic destabilization/mutation may play a pivotal role in atherosclerosis. Indeed, monoclonality of VSMCs within lesions suggests that atherosclerosis may be characterised by a sub-population of VSMCs that undergo selective replication [9]. DNA damage can also occur in the mitochondria. Indeed, mitochondrial DNA damage correlates with the extent of atherosclerosis in human specimens and aortas from apolipoprotein E-/- mice [10].

This ‘macro’ DNA damage is also associated with biomarkers of carcinogen exposure—such as DNA adducts or modifications to specific bases in atherosclerotic plaques. ‘Bulky’ aromatic DNA-adducts in VSMCs (most likely related to environmental exposure to genotoxic chemicals) are a predictor of atherosclerosis extent in humans even after adjustment for age, smoking, obesity, heart weight and genetic susceptibility markers [11]. DNA strand breaks, oxidised pyrimidines and altered purines are also significantly higher in patients with coronary artery disease than controls [12], and human plaques show markers of oxidative damage, including DNA strand breaks, expression of 8-oxo-G (an oxidative modification of guanine residues in DNA) and activation of DNA repair enzymes [13]. Strong nuclear and cytoplasmic immunoreactivity for 8-oxo-G is detected in plaque VSMCs, macrophages and endothelial cells, but not in VSMCs of adjacent normal media or normal arteries [13]. DNA damage is also a direct correlate of extent of atherosclerosis in experimental animals. For example, cholesterol feeding of rabbits induces oxidative damage in plaques, manifested by 8-oxo-G staining [14], DNA strand breaks, and apoptosis.

1.2. Causes of DNA damage—risk factors for atherosclerosis

DNA can be damaged in numerous ways. Spontaneous damage due to replication errors, deamination, or depurination has to be repaired in addition to damage derived from oxidation and environmental chemicals. Many of the risk factors associated with atherogenesis, such as smoking and diabetes mellitus, may directly induce DNA damage. For example, smoking can cause oxidative DNA damage, inhibit DNA repair, and induce the production of advanced glycation end products, which themselves cause DNA mutation (reviewed in [15]). Similarly, advanced glycation end products have been implicated in the oxidation of low-density lipoprotein [16] and elevated levels of 8-oxo-G. Although direct damage from specific risk factors or environmental agents may contribute to DNA damage in atherosclerosis, the most likely triggers of damage are reactive oxygen species.

1.3. Cause of DNA damage in atherosclerosis—reactive oxygen species

It has been estimated that approximately $2 \times 10^4$ DNA damaging events occur in every cell/day [17]; a major portion of these occur via reactive oxygen species (ROS) [18]. ROS include the superoxide anion ($\cdot O_2^-$), hydrogen peroxide, hydroxyl radical, peroxynitrite and lipid peroxides (Fig. 1), with their reactivity and half-life varying according to species. ROS are constantly produced within the cell, in particular via mitochondrial oxidative metabolism and pathological processes such as inflammation [18]. In vascular cells, the primary source of ROS may be xanthine oxidase and NAD(P)H oxidases (Noxs) [19,20]. Other sources of ROS include cytochrome P450 isoenzymes, lipoxygenase, cyclooxygenase, hemoxygenase, and glucose oxidase. Myeloperoxidase is also produced by invading macrophages (reviewed in [21]). ROS are also secondary messengers in specific signalling pathways, generated by specific plasma membrane oxidases in response to growth factors and cytokines.

DNA lesions caused by ROS include double- and single-stranded breaks (DSBs and SSBs), DNA–DNA and DNA–protein cross links and base modifications, including thymine glycol, 8-hydroxyguanine and 8-oxo-guanine. Certain types of damage can be traced back to specific insults. Whilst superoxide and hydrogen peroxide are normally not reactive to DNA, both can be converted to the extremely reactive hydroxyl radical via the Fenton reaction. The hydroxyl radical can induce a vast array of damage to both nuclear and mitochondrial DNA [22]. Hydroxyl radicals may induce base or nucleotide loss, adducts, and single- and double-strand breaks. In particular, hydroxyl radicals can interact with pyrimidine double bonds causing glycolytic damage (e.g. thymine glycol, uracil glycol) that can cause mis-pairing, transcriptional interrupts and, if left un-repaired, induce cell cycle arrest. Similarly,
interaction of OH radicals with purines will generate formamidopyrimidines and other purine oxidative products that are usually recognised by the DNA repair mechanism. Thymidine oxidation, or the addition of methyl and alkyl groups, is frequently attributed to ROS of all types. Interestingly, 8-oxo-G, which frequently causes oxidative damage to deoxyguanines, is not recognised by the DNA repair system and is thus highly deleterious to cells. Unrepaired 8-oxo-G will mis-pair with dA, leading to an increase in G to T transition mutations.

The cell has a number of mechanisms of protection against oxidative damage (reviewed in [23]), including direct interaction with antioxidants such as α-tocopherol, ascorbic acid and glutathione (scavengers). Glutathione exists in both its oxidised form (GSSG) and reduced (GSH) forms, and can function alone or in association with enzyme activities. In addition, antioxidant enzymes are present such as superoxide dismutases (which convert the superoxide radical to hydrogen peroxide and water), and glutathione S transferases that conjugate reduced GSH to hydrophobic organic compounds such as lipid peroxides. In general, the balance between ROS levels and the activity of these defence mechanisms determines the degree of oxidative stress encountered by the cell.

1.4. Evidence for oxidant stress in atherosclerosis

Increased levels of ROS are found in all layers of the atherosclerotic arterial wall, and particularly in the plaque itself [24]. Although ROS are associated with upregulation of several vascular NAD(P)H oxidase subunits and increased enzyme activity [25], confirmation of the role of ROS in atherosclerosis comes from studies with genetic disruption of the p47phox subunit of NAD(P)H oxidase, which causes dramatic inhibition of atherogenesis in ApoE<sup>−/−</sup> mice [26]. Increased levels of xanthine oxidase and reduced ecSOD are found in coronary arteries and plasma of patients with coronary artery disease [27]. Similarly, low levels of glutathione peroxidase activity are an independent risk factor for cardiovascular events in patients with coronary artery disease [28].

Oxidative damage to the mitochondrial genome with resultant mitochondrial dysfunction is also an important consequence of increased intracellular ROS. Hydrogen peroxide and peroxynitrite induce mitochondrial DNA damage and dysfunction in endothelial cells and VSMCs, with endothelial cells being particularly sensitive [29]. As mentioned above, mitochondrial DNA damage correlates with the extent of atherosclerosis in human specimens and aortas from ApoE<sup>−/−</sup> mice, whilst disruption of manganese superoxide dismutase, a mitochondrial antioxidant enzyme, show increased mitochondrial DNA damage and accelerated atherogenesis at arterial branch points [10].

2. The DNA damage response pathway

The plethora of DNA damage lesions in cells is rapidly detected by a complex web of signalling pathways called the DNA damage response pathway. This pathway involves three groups of evolutionarily conserved proteins, which act in concert to translate the DNA damage signal into a specific cellular response (Figs. 2 and 3). These are:

1. Sensors: recognise the lesions themselves or chromatin alterations that follow DNA damage. Examples include the MRN and 9–1–1 complexes.
2. Transducers: initiate a signal transduction cascade that propagate and amplify the signal. Examples include ATM and ATR.
3. Effectors: execute the specific cellular response. Examples include ChK1 and ChK2.

2.1. Sensors

2.1.1. MRE11–RAD50–NBS1 (MRN)

Double-stranded DNA breaks (DSBs) may cause chromosomal aberrations and disrupt genetic integrity, leading to carcinogenesis. DNA replication errors are the major cause of DSBs in dividing cells, although they may also arise from ionising radiation and genotoxic agents. The two mechanisms for DSB repair are homologous recombination between sister chromatids and the rapid, error prone non-homologous end joining[30]. The MRN complex plays a key role in the cellular response to DSBs[31] as well as other aspects of DNA metabolism such as telomere maintenance[32]. The MRE11 protein has an amino terminal phosphoesterase domain and two DNA binding sites. The phosphoesterase domain not only contains the NBS1 binding site, but also functions as both a single and double stranded DNA endonuclease as well as a 3'-5' double strand exonuclease[33]. RAD50 contains a bipartite ATP binding cassette joined by two coiled-coil domains, with a Cys-X-X-Cys motif located in the middle of the coiled-coil domain, which serves as a dimerization domain[34]. NBS1 is essential for the nuclear transportation of the MRN complex and binding of phospho-H2AX, and is responsible for MRN recruitment to sites of DSBs[35].

The key role of the MRN complex in the DSB response has been emphasized by genetic studies. Hypomorphic mutations in MRE11 lead to ataxia–telangiectasia-like disease, which like ataxia–telangiectasia (A–T—see below), includes progressive cerebellar degeneration, hypersensitivity to ionising radiation and radioresistant DNA synthesis[36]. Hypomorphic mutations in NBS1 lead to the Nijmegen breakage syndrome (NBS), which is characterised by microcephaly, mental deficiency, immunodeficiency, hypersensitivity to irradiation, chromosomal instability and cancer predisposition. A variant of this disease is caused by RAD50 mutations.

The similarities noted amongst ataxia–telangiectasia, ataxia–telangiectasia-like disease, and NBS suggest a functional link between MRN and ATM. This link is complex and is explained by a two-step model in which
NBS1 is firstly recruited to sites of DSB by binding to MRE11 in an ATM-dependent manner. ATM activation and phosphorylation of its downstream targets such as γ-H2AX are thought to assist in the recruitment and retention of further MRN molecules by NBS1–γ-H2AX interaction [37].

2.1.1.1. Rad9–Rad1–Hus1 (9–1–1). The 9–1–1 complex is present in the nucleus of both damaged and undamaged cells. The complex resembles the proliferating nuclear antigen, a doughnut shaped homotrimeric complex, which forms a sliding clamp at sites of DNA replication and serves as a sliding platform for the accumulation of the replicative machinery [38]. The 9–1–1 complex is loaded around the DNA by the Rad17-replication factor C in response to genotoxic stresses such as ionising radiation, UV light and replication inhibitors [39]. The 9–1–1 complex is involved in the ATR/ChK1 signalling axis [40] and is loaded onto DNA following single strand DNA damage. The Rad9 tail, which contains a consensus phosphatidylinositol 3-kinase (PIKK) site, is then phosphorylated by ATR and in turn facilitates the phosphorylation and activation of ChK1 [41].

2.2. Transducers

The two main transducers of DNA damage in mammals are ATM (ataxia–telangiectasia gene product) and ATR (ATM and Rad3-related) [42]. Both are members of the phosphatidylinositol 3-kinase-like family of serine/threonine protein kinases (PIKK) [42]. ATM functions particularly after DSBs, ATR after SSBs and separate N-glycosylases function in base excision repair.

2.2.1. ATM

ATM deficiency leads to ataxia–telangiectasia (A–T), an autosomal recessive syndrome with early childhood onset of progressive cerebellar ataxia, ocucalcutaneous telangiectasia, primary immunodeficiency (decreased IgA, IgE, and IgG2), retarded somatic growth, premature ageing, and predisposition to lymphoreticular malignancy [43]. In addition, these patients exhibit chromosomal aberrations, cell cycle checkpoint defects and increased rates of telomere shortening [44,45]. Patients with two mutant alleles develop new cases of cancer at approximately 100 times the age-specific population rate and have a median age of death of approximately 20 years.
Over 400 different ATM mutations have so far been identified of which more than 85% are null mutations resulting in no detectable ATM protein [46,47]. A–T heterozygotes comprise approximately 1.4–2% of the general population [48]. ATM carriers have an increased risk of cancer, but also of ischaemic heart disease [49,50], dying on average 7–8 years earlier. Importantly, the effect of ATM carrier status on cardiovascular mortality is similar to that of smoking or male gender. Although this suggests that ATM carriage may account for a significant proportion of the genetic inheritance of coronary artery disease, the mechanism by which ATM heterozygosity promotes coronary artery disease is unknown.

ATM is located within the nucleus of most cells as dimers or higher order multimers with the kinase domain of each molecule being blocked by the other [51]. In response to DSBs, each ATM molecule phosphorylates the other on ser1981 leading to monomerisation and activation of ATM [51]. The active ATM molecules are then recruited to DSB sites, an event which is facilitated by the MRN complex, serving as a platform for further enzymatic reactions [52] as well as initiating phosphorylation events leading to regulation of specific cell cycle checkpoints [53]. The main target for ATM in this pathway is the tumour suppressor gene p53, which is phosphorylated on ser15 [54–56], enhancing its transcriptional activity [57]. ATM also phosphorylates and activates ChK2, which in turn phosphorylates p53 on ser395 [58], and interferes with the p53–MDM2 interaction. Finally, ATM directly phosphorylates MDM2 on ser395 thereby inhibiting the nuclear export of the p53–MDM2 complex and the subsequent degradation of p53 [59]. The ATM mediated modulation of p53 is an illustrative example of the numerous mechanisms by which ATM can regulate a single protein within the same pathway.

In addition to its critical role in cell cycle checkpoints, and maintenance of telomere length and integrity [60], A–T cells show abnormal responses to oxidant stress and increased oxidative stress is evident in A–T. For example, A–T fibroblasts are more sensitive to oxidant stress-induced DNA damage than normal cells [61], and have constitutive activation of DNA damage repair pathways that are reversed in part by antioxidants [62]. Oxidant stress can induce ATM kinase activity, which in normal cells is associated with cell cycle arrest in G1 and G2/M; indeed, ATM is required for growth arrest after oxidative stress [63]. In addition, tissues from ATM knockout mice show increased oxidative stress, including elevated levels of 3-nitrotyrosine [64], lipid peroxidation [64], and accumulation of superoxide and hydrogen peroxide [65]. Whilst the most striking effects are seen in the brain, patients with A–T show reduced total plasma antioxidant capacity, suggesting that they may sustain constant systemic oxidative stress [66].

2.2.1.1. ATR. ATM-mediated pathways are not completely abolished in A–T cells, but are rather dampened and turned on slowly. This indicates the presence of parallel kinases, which act in concert with ATM. One such system is ATR, which can phosphorylate ATM substrates albeit with much slower kinetics [67]. ATR responds to UV-light, stalled replication forks and hypoxia [53]. The recruitment of ATR to DNA lesions is facilitated by the ATR interacting protein. This is accompanied by phosphorylation of some ATM substrates such as p53 [68] as well as ATR-specific targets such as ChK1 and RAD17 [69]. Mice lacking ATR die in the early stages of embryogenesis and ATR deficiency is not compatible with cellular viability in culture [70]. This is because the ATR–ChK1 axis is fundamental in S phase, preventing the progression of damaged DNA and hence preventing mitotic catastrophe. Mutations causing partial loss of ATR activity in humans have been associated with the autosomal recessive disorder Seckel syndrome, which shares features in common with A–T [71].

2.3. Effectors

2.3.1. ChK1

The ChK1 protein consists of a kinase domain and an SQ domain, containing multiple phosphorylation sites. ChK1 is present in an active form during the S and G2 phases of the cell cycle even in the absence of DNA damage [72], but is activated in response to DNA damage and stalled replication forks by ATR, which phosphorylates ChK1 at ser317 [72]. Mice lacking ChK1 die early in embryogenesis [73] and embryonic stem cells lacking ChK1 are not viable in culture [74]. In human cells, ChK1 is essential in Cdc25A metabolism as well as the checkpoint response to ionising radiation and DNA damaging agents [75].

2.3.2. ChK2

The ChK2 protein contains multiple ATM recognition sites and both dimerization and kinase domains. ChK2 is expressed throughout the cell cycle and is inactive in the absence of DNA damage [76]. Following DNA damage and ATM activation, ChK2 is phosphorylated at thr298 and forms a homodimer [77]. Mice deficient in Chk2 are viable, fertile and exhibit increased resistance to ionising radiation [74]. In humans, mutations in Chk2 are associated with a spectrum of malignancies including the Li Fraumeni syndrome [78], breast and colon cancer [79].

The ATM/Chk2 and ATR/Chk1 pathways are no longer considered as parallel branches of the DNA damage response pathway, but rather a system where there is a high degree of cross talk and connectivity. For instance, ATM can activate Chk1 in response to ionising radiation, and Chk2 can be activated independently of ATM [80].

3. Effects of DNA damage in atherosclerosis

DNA damage to cells of the vessel wall may have a number of effects. However, the most likely consequences are cell senescence, cell death and DNA repair.
3.1. Cell senescence

Extensive characterisation of lesion development has shown that cell proliferation is low in early atherosclerosis (Fatty streak, Stary Type I lesion), peaks in the intermediate lesions (Stary II–IV), and declines in advanced fibroproliferative, complicated plaques (Stary V lesions) [81,82]. In vitro studies have confirmed that plaque VSMCs show reduced cell proliferation rates, increased population doubling times, and earlier failure to proliferate (senescence) than medial VSMCs [83]. Cell senescence may be triggered by two broadly different mechanisms. Replicative senescence may be induced by reduction of telomere length, changes in structure such as telomeric fusion or dicentrics, or loss of telomere-bound factors. Telomeres may trigger growth arrest via DNA damage responses at critical telomere lengths or structure. Cells subjected to sub-lethal stress due to DNA damage (UV and γ-irradiation, oxidative stress and treatment with histone deacetylase inhibitors) also undergo ‘stress-induced premature senescence’ (SIPS). SIPS resembles replicative senescence, cells demonstrating a similar morphology and pattern of cell cycle regulators.

ROS can induce both telomere-based senescence and SIPS. ROS induce DNA strand breaks, and base and nucleotide modifications, particularly in sequences with high guanosine content [84], such as telomeres. Indeed, telomeres are one of the DNA structures most sensitive to oxidative damage [85] and ROS can accelerate telomere loss in vitro [86]. Increased telomere loss/division can also occur in individual cells due to a telomere-specific deficiency in base excision repair, leading to preferential accumulation of ROS-induced single-stranded DNA breaks [85] preventing replication of distal telomeres when cells divide. Thus, it is possible that oxidative DNA damage to telomeres induces a DNA repair response that induces senescence. Not only do ROS induce senescence, but also senescent cells produce high levels of ROS, and contain higher levels of oxidatively damaged DNA [87]. In vitro, VSMCs from aged mice have decreased proliferation, yet generated higher levels of ROS in comparison with cells from younger mice, associated with decreased endogenous antioxidant activity, increased lipid peroxidation, and mitochondrial DNA damage [88].

3.2. Cell death

In cells where the DNA damage is too much to repair, or in cells that are driven to proliferate, DNA damage induces apoptosis. Apoptosis is evident in endothelial cells, macrophages and VSMCs in atherosclerotic plaques. Endothelial cell death is implicated in both atherogenesis and plaque erosion [89], whereas VSMC death may promote thinning of the fibrous cap and plaque rupture. Indeed, increased levels of VSMC apoptosis are seen in mature plaques when compared to control vessels [90], and in unstable versus stable plaques or patients [91,92]. Cell death can be induced by ROS and oxidised lipids in vascular cells, whereas p53 expression in an experimental neointima can induce apoptosis and promote plaque rupture [93].

3.3. DNA repair

Although there is evidence of activation of DNA repair pathways in human atherosclerosis, cells displaying DNA damage are much more frequent than cells displaying markers of apoptosis, implying that repair occurs to prevent death [13]. In human plaques markers of DNA damage are associated with activation of base excision repair or nonspecific repair pathways [13]. In cholesterol-fed rabbits plaques also manifest DNA damage associated with upregulation of DNA repair enzymes [14]. In these studies, DNA strand breaks normalized after 4 weeks of dietary lipid lowering, but a significant reduction of 8-oxo-G immunoreactivity was only observed after a prolonged period of lipid lowering, emphasizing the longevity of DNA damage in atherosclerosis. In addition, repair pathways started to decline progressively when cholesterol-fed animals were placed on a normal diet [14]. These studies demonstrate that DNA damage and activation of repair pathways occur in atherosclerosis, and are also reversible, at least in the early stages of atherosclerosis.

4. Prevention/treatment of DNA damage in atherosclerosis

The presence and biological consequences of DNA damage in atherosclerosis mean that both prevention and reversal of damage are therapeutic aims. In vitro, antioxidants can ameliorate ROS-induced DNA damage, although antioxidant trials in humans have been disappointing. In contrast, cholesterol lowering by diet is associated with a reduction in DNA damage and markers of DNA repair, at least in animal models. Drugs that have been proven to alter plaque progression and patient events have also been shown to alter vascular oxidative stress. In particular, HMGCoA reductase inhibitors (‘Statins’) reduce NAD(P)H oxidase activation [94,95] and superoxide production in vitro, in part by inhibiting the membrane translocation (and thus activity) of the small GTP-binding protein Rac-1 [96,97], a regulatory component of vascular NAD(P)H oxidase. Statins can also reduce superoxide production, and mRNA expression of specificnox subunits in vivo [96,98]. This effect may underlie the observation that atorvastatin reduces the degree of DNA damage of peripheral lymphocytes as well levels of oxidant stress in hyperlipidaemic patients [99].

5. Conclusions

DNA damage is increasingly recognised as being present in all cells within the atherosclerotic plaque. DNA damage
may promote atherogenesis, and in advanced lesions induce phenotypic changes such as cell senescence and cell death that promote unstable plaques. Knowledge of both the triggers of DNA damage and the pathways underlying the DNA damage responses should lead to both prevention and treatment of DNA damage in atherosclerosis.

Acknowledgements

MM, JM and MB are supported by British Heart Foundation Grants FS/05/008 and RG/04/001.

References


