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DNA Damage in Carotid Artery Stenosis

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Abstract

Carotid Artery Stenosis (CAS) is a common vascular disease affecting the elderly health in the world. Surgery is the most effective treatment for CAS, but the high restenosis rate limits the long-term success. The molecular mechanisms of CAS and restenosis is still unclear. Multiple studies have shown that DNA damage and repair present in atherosclerosis and CAS, but their relevance to the development of CAS remain unknown. In this review, we summarized the research status of DNA damage in the development and treatment of CAS..

Keywords: Carotid artery stenosis; Restenosis; DNA damage; Atherosclerosis

Abbrevations: CAS: Carotid Artery Stenosis; ROS: Reactive Oxygen Species; NADP: Nicotinamide Adenine Dinucleotide Phosphate; VSMCs: Vascular Smooth Muscle Cells; ECs: Endothelial Cells; ACEI: Angiotensin Converting Enzyme Inhibitor; IR: Ionizing Radiation

Introduction

CAS is a major cause of ischemic stroke and cardiovascular disease. At present, the most effective treatment for CAS is carotid endarterectomy or carotid artery stenting, but the high restenosis rates limit the long-term success [1,2]. Atherosclerosis is the pathology basis of CAS; intimal hyperplasia is thought to be the main cause for restenosis [3-5]. The pathogenesis of CAS has been widely studied in past decades. However, the molecular mechanisms of CAS and restenosis have not been clearly understood.

DNA damage is the destruction of DNA structure that could be generated from DNA replication or a consequence of internal and external stimulus, at a frequency of 104 times per single cell per day [6]. In recent years, a number of studies demonstrated that DNA damage and repair is present in atherosclerosis and CAS [7,8]. DNA damage response involve in a variety of cellular processes including cell cycle control, cell senescence and apoptosis, which may directly or indirectly affect the atherosclerotic formation and intimal hyperplasia [9]. In this review, we summarized the current knowledge about DNA damage in the development and treatment of CAS.

Stimuli that cause DNA damage in carotid artery

Stimuli in vascular that cause DNA damage can be divided into two classes based on its origin: endogenous and exogenous. The major endogenous stimulus is Reactive Oxygen Species (ROS), that can be generated from normal cellular metabolism [10-12], and exogenous stimuli include physical and chemical agents from outside or intracavitary.

ROS can be produced by multiple enzymes in cells, such as Nicotinamide Adenine Dinucleotide Phosphate (NADP) oxidase, lipoxygenases, xanthine oxidase and mitochondrial enzymes [13]. NADPH oxidases is thought to be the most important ROS generation system in vascular, the laminar shear stress generated by blood flow, inflammation, growth factor and cytokine in blood act as catalyzer for NADPH oxidases and promotes ROS generate [14]. ROS at normal levels is an important cellular messenger and participates in immune response. However, excessive ROS in vascular under pathological conditions can add double bonds or remove hydrogen atoms from the DNA bases, resulting in many types of DNA damage, such as mitochondrial DNA damage, bases damage, single-strand break and double-strand break [15]. The extensive expression of 8-hydroxy2-deoxyguanosine (8-OHdG) and 7,8-dihydro-8-oxo-2-deoxyguanosine (8-oxo-dG), two oxidative DNA damage markers [16], is a common feature for advanced atherosclerosis lesions. Moreover, ROS in vascular acts directly on Vascular Smooth Muscle Cells (VSMCs) and promotes proliferation and migration, which are the key mechanism of intimal hyperplasia [17].

There is growing evidence suggesting that DNA damage-inducing treatment is related to artery stenosis. Clinical studies have shown that the increased incidence of ischemia stroke in

testicular cancer, breast cancer and Hodgkin's lymphoma patients is associated with radiation therapy and chemotherapy [18-20]. Stewart F et al. [21] demonstrated that ionizing radiation accelerates the development of atherosclerotic lesions in ApoE-/- mice by promoting the aggregation of inflammatory cells in atherosclerotic plaques [21]. In patients with malignant tumor, radiation and chemotherapy may directly or indirectly induce DNA damage in carotid artery. Energy carried by ionizing radiation may deposite on DNA bases and directly induce SSBs and DSBs [22]. Also, radiation cause water ionization and produce hydroxyl to induce DNA damage indirectly [23]. Cytotoxic agents cause DNA damage through different pathways. For example, alkylation agents directly destroy DNA structure by interacting with DNA chain through active groups, and antimetabolites inhibit DNA synthesis by interfering with nucleotide metabolism.

DNA damage in the development of CAS

DNA damage and repair associated proteins appears in the early stage of atherosclerosis, and the markers of DNA damage persist in cells of atherosclerotic plaques and increase in advanced lesions [12,24], which could be the consequence of persisting stimuli or DNA damage repair deficiency is still unclear. A previous study showed the deficiency of homologous recombination, a major and highly conserved DSB repair pathway, in carotid artery tissues from patients with carotid restenosis [7]. Another study by Martin B, et al found that defective base excision repair for 8-oxoguanine oxidative lesion in atherosclerotic plaque Vascular Smooth Muscle Cells (VSMCs), due to the reduced acetylation of OGG1, accelerates the development of atherosclerosis [25]. These findings raise an important question of whether we can prevent the atherosclerosis by improvement the DNA repair efficiency. A recent study compared the formation of atherosclerotic plaques in two groups of ApoE-/- mice that overexpress wild type and C-terminal deleted NBS1 in the VSMCs respectively, NBS1 would accelerate DSB repair and C-terminal deleted NBS1 delay repair, the overexpression of NBS1 in VSMCs enhanced DSB repair and improved the stability of plaques compare to another group but did not slowed the atherogenesis [26]. Therefore, the efficiency of DNA damage repair may have minimal effects on atherogenesis but may underlie some of the therapeutic benefits in preventing plaques rupture, especially in CAS.

Although there is no solid evidence that DNA damage directly influence atherogenesis and intimal hyperplasia, it has been shown that the consequences of DNA damage associate with CAS. DNA damage induces the cell cycle arrest by activating DNA damage checkpoints, which will guarantee proper time for DNA repair [27,28]. Inefficient DNA repair will sustain low level of checkpoint activation and result in cell senescence and apoptosis [29]. Mover, the CHK1- and CHK2- dependent activation of p53 can induce cell apoptosis [9,30]. The senescence and apoptosis of Endothelial Cells (ECs), VSMCs and macrophages accelerate atherosclerosis, promote features of plaque vulnerability and cause inflammation [9,26,31,32]. The cytokine, interleukin, endothelin and nitric oxide released by senescent/ apoptotic cells and inflammation can induce VSMCs phenotype switch from contractile to secretory and phagocytic type, which will further promote the development of atherosclerosis and intimal hyperplasia [17,33-35].

DNA damage for CAS treatment

Reducing risk factors of atherosclerosis by pharmacotherapy is an effective and safe method for the prevention of CAS. For example, Angiotensin Converting Enzyme Inhibitor (ACEI) can suppress the inflammatory response and reduce ROS generation in arteries by inhibiting the generation of angiotensin and activate the angiotensin 2 [36]. Atorvastatin can reduce aldosterone-induced ROS generation and vascular inflammation through its inhibitory effects on Rac1/2 activation [37].

Irradiation as a treatment for suppressing intimal hyperplasia was widely studied in past decades, high dose of Ionizing Radiation (IR) can kill cells directly through inducing irreparable DNA damage [23,38]. IR or radioactive stent implantation at early stage can relieve intimal proliferation effectively [39]. The IR doses to treat intimal hyperplasia are generally in the range of 10 to 25 Gy to guarantee good therapeutic effect and low rates of complication [22].

A recent study showed that pharmacological inhibition of CHK1 significantly reduces vascular remodeling and improves hemodynamic parameters in pulmonary arterial hypertension rat model through suppressing DNA damage repair [40]. Furthermore, the inhibition of PARP-1, a DNA repair enzyme, attenuates neointima formation through inhibition of leukocyte infiltration in rat carotid artery after balloon injury [41]. These results suggest that inhibition of DNA damage repair enzyme may be potentially a strategy to prevent intimal hyperplasia.

Conclusion

ROS generated in vascular under pathological conditions is the main cause of DNA damage. Cell senescence, apoptosis and inflammation caused by DNA damage promotes atherogenesis and VSMCs proliferation, which is the major reason for CAS. Reducing the ROS generation in vascular by pharmacotherapy is an effective way for CAS prevention, the inhibition of DNA damage repair enzyme could benefit the prevention of intimal hyperplasia.

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