DNA Damage in Carotid Artery Stenosis

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Submission: September 01, 2019; Published: September 19, 2019

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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


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 10^4 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-hydroxy-2-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...
Cytokines, interleukins, 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 may benefit the prevention of intimal hyperplasia.

Acknowledgment

This work was funded by the National Natural Science Foundation of PR China Grant (B1470587 to T.L.).

References


DOI: 10.19080/JOCCT.2019.15.555902

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DOI: 10.19080/JOCCT.2019.15.555902