Complex interplay of DNA damage, DNA repair genes, and oxidative stress in coronary artery disease

Oxidative stress and DNA damage have been increasingly recognized to coexist in the setting of coronary artery disease (CAD). DNA damage is present in all cells within the atherosclerotic plaque, and there is increasing evidence that human atherosclerosis is associated with damage to DNA of both circulating cells and cells of the vessel wall. DNA damage usually includes DNA strand breaks, mutations of single bases, modified bases (including oxidation), or DNA adducts. Many of the risk factors associated with atherogenesis, such as smoking and diabetes mellitus, could directly induce DNA damage (1).

Inflammation plays a pivotal role in atherogenesis. The response is continuously mediated by monocyte-derived macrophages and specific subtypes of T lymphocytes at every stage of the disease. Granulocytes are rarely implicated because they are scarce in atherosclerotic lesions during any phase of atherogenesis (2). The action of different subsets of macrophages in atherosclerotic lesions is subsequently regulated by cytokines released by T cells. The monoclonal origin of cells from human atherosclerotic plaques is the triggering and the substantiating event for the association of DNA damage with the development of cardiovascular pathologies in the general population (3).

In addition to traditional CAD risk factors, oxidative stress has been regarded as one of the most important contributors to the progression of atherosclerosis. Oxidative stress could also constitute the major causative mechanism for DNA damage in CAD (4). Reactive oxygen species include the superoxide anion, hydrogen peroxide, hydroxyl radical, peroxynitrite, and lipid peroxides. Superoxide and hydrogen peroxide are normally not reactive to DNA, but they can be converted via the Fenton reaction to the hydroxyl radical, which is extremely reactive. The hydroxyl radical can induce a vast array of damage to both nuclear and mitochondrial DNA (1, 5). Apart from oxidative stress, inflammation is another major determinant of DNA damage along with ischemia reperfusion.

Kadıoğlu et al. (6 in this issue of AJC entitled "The role of Oxidative DNA damage, GSTM1, GSTT1 and hOGG1 gene polymorphisms in coronary artery disease risk.") provided evidence of significantly increased DNA damage in peripheral blood lymphocytes of CAD patients compared with healthy subjects, which was in agreement with previous studies (7, 8). However, they showed that DNA damage was not the result of augmented oxidative stress in those patients leaving inflammation as the most probable cause.

In atherosclerotic plaques, there is evidence of activation of DNA repair mechanisms along with signs of DNA damage. Genome lesions are eliminated with DNA strand break repair, base excision repair, and mismatch repair, whereas patients with specific polymorphisms in genes responsible for DNA repair have been found to be more susceptible to CAD (9, 10). The genotype analysis by Kadıoğlu et al. (6) revealed no clear association between the studied hOGG1 gene polymorphism and CAD. Nevertheless, the dual heterogeneity of risk factors and of the CAD patients should be noted. Therefore, further work is needed in delineating the relationship between DNA repair gene polymorphisms and CAD.

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