Enhanced base excision repair capacity in carotid atherosclerosis may protect nuclear DNA but not mitochondrial DNA

Lesional and systemic oxidative stress has been implicated in the pathogenesis of atherosclerosis, potentially leading to accumulation of DNA base lesions within atherosclerotic plaques. Although base excision repair (BER) is a major pathway counteracting oxidative DNA damage, our knowledge on BER and accumulation of DNA base lesions in clinical atherosclerosis is scarce. Here, we evaluated the transcriptional profile of a wide spectrum of BER components as well as DNA damage accumulation in atherosclerotic and non-atherosclerotic arteries. BER gene expression levels were analyzed in 162 carotid plaques, 8 disease-free carotid specimens from patients with carotid plaques and 10 non-atherosclerotic control arteries. Genomic integrity, mitochondrial (mt) DNA copy number, oxidative DNA damage and BER proteins were evaluated in a subgroup of plaques and controls. Our major findings were: (i) The BER pathway showed a global increased transcriptional response in plaques as compared to control arteries, accompanied by increased expression of several BER proteins. (ii) Whereas nuclear DNA stability was maintained within carotid plaques, mtDNA integrity and copy number were decreased. (iii) Within carotid plaques, mRNA levels of several BER genes correlated with macrophage markers. (iv) In vitro, some of the BER genes were highly expressed in the anti-inflammatory and pro-resolving M2 macrophages, showing increased expression upon exposure to modified lipids. The increased transcriptional response of BER genes in atherosclerosis may contribute to lesional nuclear DNA stability but appears insufficient to maintain mtDNA integrity, potentially influencing mitochondrial function in cells within the atherosclerotic lesion.