Novel links between oxidative DNA damage and development of inflammation

Oxidatively modified proteins, lipids, and RNA are usually subjected to degradation, whereas DNA base and strand lesions have to be repaired to reestablish genomic integrity. The primary target of ROS in DNA is guanine due to its lowest redox potential among DNA bases. Although the spectrum of guanine base lesions varies according to the nature of oxidants, 7,8-dihydro-8-oxoguanine (8-oxoG) is the most frequent oxidation product of DNA. In mammals, the intra-helical 8-oxoG is recognized by its unique electronic properties and excised by the 8-oxoguanine DNA glycosylase 1 (OGG1) from nuclear and mitochondrial genomes during base excision repair (BER) processes. The resulting free 8-oxoG base is thought to lack biological role and it is excreted from cells and organisms. Unrepaired 8-oxoG may be paired with adenine during DNA replication, resulting in transversion mutations. Despite accumulation of 8-oxoG in the genome, OGG1 knock out (*Ogg1*$^{-/-}$) mice have no marked phenotypic changes or significant tumor predisposition, even after chronic oxidative stress exposures. Unexpectedly, *Ogg1*$^{-/-}$ mice have an increased resistance to inflammation after *H. pylori* infection or treatment with LPS or oxazolone suggesting a DNA repair-independent function of OGG1 and/or the free 8-oxoG base in the development of inflammation. Indeed, a lack of 8-oxoG repair by OGG1 in airway epithelium decreased allergic inflammation in a mouse model of asthma (Bacsi et al. 2013). In a recent series of experiments, it has been described that OGG1 can exert non-repair functions after binding its excised product, 8-oxoG (Boldogh et al. 2012). It has been demonstrated that OGG1 has a non-catalytic binding site for 8-oxoG. In a complex with its product, OGG1 not only becomes more efficient removing oxidized guanine, but also goes through sterical changes, which enable its physical interaction with small GTPases, Ras (Boldogh et al. 2012), Rac1 (Hajas et al. 2013) and Rho (Luo et al. 2014) proteins. These interactions result in GDP to GTP exchange activating these small GTPases. It has been revealed that OGG1/8-oxoG complex formation can lead to MEK/ERK phosphorylation via Ras, a NOX4-mediated increase in cellular ROS levels via Rac1 or α-smooth muscle actin polymerization into stress fibers via Rho. Furthermore, recent observations have indicated that NF-κB driven gene expression requires enrichment of 8-oxoG and oxidatively modified OGG1 in the promoter sequences after TNF-α exposure of cells. OGG1 bound to 8-oxoG facilitates NF-κB's DNA occupancy. OGG1 depletion decreased both NF-κB's association with promoter and cellular transcriptional response to TNF-α challenge (Pan et al. 2016).