NEW KID ON THE BLOCK: UNEXPECTED ROLES OF 8-OXOGUANINE DNA GLYCOSYLASE-1 IN THE CELLULAR RESPONSES

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Introduction: 8-Oxo-7,8-dihydroguanine (8-oxoG) is one of the most abundant DNA base lesions induced by reactive oxygen species (ROS). Accumulation of 8-oxoG in the mammalian genome is considered a marker of oxidative stress, to be causally linked to inflammation, and is thought to contribute to aging processes and various aging-related diseases. 8-OxoG is excised from DNA by 8-oxoguanine DNA glycosylase-1 (OGG1) during DNA base excision repair (BER); the resulting exogenomic 8-oxoG base is thought to have no biological role, and is excreted from cells and organisms. Unexpectedly, mice that lack 8-oxoguanine DNA glycosylase-1 (OGG1) activity and accumulate 8-oxoG in their genome have a normal phenotype and longevity; in fact, they show increased resistance to both oxidative stress and inflammation.
Methods: Human diploid fibroblasts (MRC5), HeLa S3 cervical epithelial cells, A549 type II alveolar epithelial cells, U937 monocytic lymphoma cells, KG-1 myeloid leukemia cells expressing a temperature-sensitive mutant OGG1, mouse models of airway inflammation, siRNA ablation of gene expression, and a variety of molecular biological assays were utilized to define a link between OGG1-BER and cellular signaling.
Results: It has been demonstrated that OGG1 binds its repair product 8-oxoG base with high affinity at a site independent from its DNA lesion-recognizing catalytic site and the OGG1•8-oxoG complex physically interacts with GDP-bound Ras and Rac1 proteins. This interaction results in a rapid GDP→GTP, but not a GTP→GDP, exchange. Importantly, a rise in the intracellular 8-oxoG base levels increases the proportion of GTP-bound Rac1. Exogenously added 8-oxoG base is able to enter the cells and increase the proportion of both GTP-bound Ras and Rac1. In turn Rac1-GTP mediates an increase in ROS levels via nuclear membrane-associated NADPH oxidase type 4. Activation of Ras GTPase results in phosphorylation of the downstream Ras targets Raf1, MEK1,2 and ERK1,2. Ogg1 silencing in the airway epithelium decreases TNF-α-induced expression of chemokines/cytokines including Cxcl-2 and neutrophil recruitment. Silencing of OGG1 expression hampers TNF-α-induced association of transcription factors with promoter sequences and lowers Cxcl-2 expression. Furthermore, decreased Ogg1 expression in the airway epithelium conveys a lower inflammatory response after ragweed pollen challenge of sensitized mice.
Conclusions: These findings reveal novel mechanisms by which OGG1 in complex with 8-oxoG is linked to redox signaling and cellular responses. Results from *in vivo* studies indicate that a transient modulation of OGG1 expression/activity in airway epithelial cells could have clinical benefits.