

Nitric oxide, DNA damage and genome integrity in *Trypanosoma brucei*: role of uracil-DNA glycosylase.

Miriam Yagüe Capilla, Daniel García-Caballero, María Valente, Luis M. Ruiz-Pérez, Antonio E. Vidal, Víctor M. Castillo-Acosta, and Dolores González-Pacanowska. Instituto de Parasitología y Biomedicina “López-Neyra”. CSIC. Granada, Spain.

During infection, an essential component of the primary immune response is the production of nitric oxide (NO) by the inducible nitric oxide synthase of activated phagocytes. However, the impact of NO on the progression of African trypanosomiasis is still unclear. The reaction of NO with oxygen radicals gives rise to reactive nitrogen species that generate multiple damage in DNA thus triggering mutagenesis and genome instability, as well as other detrimental effects on proteins and lipids. The base excision repair (BER) pathway plays a pivotal role in counteracting DNA lesions through the removal of defective bases. Uracil-DNA glycosylase (UNG) is the first enzyme of BER responsible for uracil cleavage from DNA. By characterising the formation of strand breaks, the mutation rate and spectra, the uracil and abasic sites content and the number of γ H2A repair foci we show that NO exposure has a significant impact on DNA integrity in *Trypanosoma brucei*. Parasites lacking UNG exhibit an increased uracil content as well as a higher number of γ H2A repair foci compared to the parental line upon treatment with DETA-NO *in vitro*. We also report the increased occurrence of uracil and DNA damage in wild-type and UNG knock-out parasites recovered from infections *in vivo* thus indicating that exposure to the primary immune response has an impact on parasite DNA integrity and that base excision repair has an important role in this process.