O-05 ANTI-INFLAMMATORY EFFECT OF 8-HYDROXY-2'-DEOXYGUANOSINE VIA RAC SUPPRESSION IN BALB/C MICE

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8-Hydroxy-2'-deoxyguanosine (oh8dG) was believed to be carcinogenic. With the exception of our report showing that 8-hydroxyguanosine triphosphate (oh8GTP) affects the activity of small GTPase in vitro, there are no reports showing these chemicals to have other physiological effects. This study examined whether or not oh8dG inhibits the activation of Rac and the immune response in vivo. In human neutrophils stimulated by LPS, oh8dG inhibited the oxidation of NADPH, the production of reactive oxygen species, and the activation of Rac 1 and 2. The serum levels of the pro-inflammatory cytokines, TNF-α, IL-6, IL-12p70, and IL-18 were reduced in Balb/c mice that had been pretreated with oh8dG and then challenged with 1 mg/kg LPS b.w.. oh8dG inhibited the thickening of the interstitium of the lung, and the infiltration of neutrophils into the tissue, which was highlighted by the reduced number of infiltrates and myeloperoxidase activity. oh8dG inhibited the Rac 1 and 2 activity of the lung tissue. Moreover, oh8dG inhibited the translocation of the transcription factor, NF-κB (p50), and the phosphorylation of AP-1 (c-jun). Pretreating Balb/c mice with oh8dG delayed the onset of septic death induced by LPS and increased the survival rate. However, oh8dG had no significant effect on the activity of Cox or 8-oxoguanine glycosylase in the lung tissue. These suggest that oh8dG inhibits the immune response through Rac and that oh8dG can be developed as an anti-inflammatory agent without the adverse side effects associated with Cox inhibitors.
Key Words: 8-Hydroxy-2'-deoxyguanosine, Rac, LPS, Septic death, OGG1

O-06 TRANSLESION SYNTHESIS ACROSS BULKY N2-GUANINE DNA LESIONS BY HUMAN DNA POLYMERASES

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N2 position of guanine is one of the major sites for DNA modification by various carcinogens including heterocyclic aromatic amines and polycyclic aromatic hydrocarbons. Even N2-EtG induces replication error and severe block in DNA replication by bacteriophage T7 (exo-) and HIV-1 RT. TLS (translesion synthesis) DNA pols are able to replicate through bulky DNA lesions where replicative pols stalled. Oligonucleotides with varying adduct bulk at guanine N2 were analyzed for catalytic efficiency and fidelity with human DNA polymerases. Pol delta bypassed adducts effectively up to N2-EtG in an error-free manner but was strongly blocked by N2-IbG and larger adducts. Pol eta effectively bypassed adducts up to N2-NaphG but was severely blocked at N2-AnthG and N2-BPG. Pol iota effectively bypassed adducts up to N2-BzG with low fidelity but severely blocked at N2-NaphG and larger adducts. In contrast, pol kappa readily bypassed N2-G adducts up to N2-AnthG with a little retardation by N2-BPG, with the highest fidelity and efficiency among polymrases tested. Kinetic analysis opposite N2,N2-diMeG and N2-EtG indicates that N2 hydrogen is critical for the efficient and accurate bypass opposite N2-G adducts by pol eta and kappa but not by pol iota. In conclusion, TLS DNA pols are required for the efficient bypass of pol delta-blocking N2-G adducts (>N2-EtG) either in error-prone or erro-free manners and pol kappa might play a key antimutagenic role against bulky carcinogen-bound N2-G lesions in human cells.
Key Words: N2-G DNA lesion, DNA polymerase, TLS (translesion DNA synthesis), DNA adduct, Carcinogen