

PARG ACTIVITY MEDIATES POST-TRAUMATIC INFLAMMATORY REACTION AFTER EXPERIMENTAL SPINAL CORD TRAUMA

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The aim of the present study was to examine the role of poly (ADP-ribose) glycohydrolase (PARG) on the modulation of the inflammatory response and tissue injury associated with neurotrauma. Spinal cord trauma was induced in WT mice by the application of vascular clips (force of 24 g) to the dura via a two-level T6-T7 laminectomy. Spinal cord injury in WT mice resulted in severe trauma characterized by edema, neutrophil infiltration, and cytokine production followed by recruitment of other inflammatory cells, production of a range of inflammation mediators, tissue damage, apoptosis and disease. The genetic disruption of the PARG gene in mice or the pharmacological inhibition of PARG with GPI 16552 (40 mg/kg intraperitoneally bolus), a novel and potent PARG inhibitor, significantly reduced the degree of spinal cord inflammation and tissue injury (histological score), neutrophils infiltration, cytokines production (TNF- α and IL-1 β) and apoptosis. In a separate experiment we have clearly demonstrated that PARG inhibition significantly ameliorated the recovery of limb function. Taken together, our results indicate that PARG activity modulates the inflammatory response and tissue injury events associated with spinal cord trauma and participate in target organ damage under these conditions.