POLY(ADP-RIBOSE) POLYMERASE-1 AND SEPSIS PROGRESSION

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Poly(ADP-ribose) polymerase-1 is a nuclear enzyme present in eukaryotes. The primary PARP-1 functions as a DNA damage sensor and signaling molecule binding to both single- and double stranded DNA breaks. Upon binding to damaged DNA mainly through the second zinc-finger domain, PARP-1 forms homodimers and catalyzes the cleavage of NAD^+ into nicotinamide and ADP-ribose and then uses the latter to synthesize branched nucleic acid-like polymers poly(ADP-ribose) covalently attached to nuclear acceptor proteins. ATP and NAD^+ are important determinants of the mode of cell death. From these observations, it was plausible to hypothesize that PARP as a NAD^+-catabolizing enzyme may serve as a molecular switch between apoptosis and necrosis. The production of superoxide has been previously recognized as an important cytotoxic factor contributing to vascular damage in various pathophysiological conditions. Recent evidence suggests that the reaction of superoxide with NO yields a toxic oxidant, peroxynitrite, which plays a central role in the pathophysiology of inflammation and oxidant stress. Furthermore, under conditions of oxidative stress, NO may be converted to the more toxic nitroxyl anion. Oxidant stress generates DNA single-strand breaks. DNA strand breaks then activate PARP, which in turn potentiates NF-κB activation and AP-1 expression, resulting in greater expression of the AP-1- and NF-κB-dependent genes. Generation of C5a in combination with increased endothelial expression of ICAM-1, recruits a greater number of activated leukocytes to inflammatory foci. **Keywords: sepsis, PARP, DNA damage**