Presence of PARP Confirmed in Ejaculated Human Sperm

Low levels may be related to poor sperm quality, male infertility

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Failure to conceive naturally or with assisted reproduction despite the presence of morphologically normal motile sperm may be caused by poor sperm quality. Poor quality sperm includes DNA-damaged and apoptotic sperm.

Poly (ADP-ribose) polymerases (PARP) constitute a large family of 18 proteins. Poly (ADP-ribose) metabolism is critical in a wide range of biologic processes, including DNA repair and maintenance of genomic stability, transcriptional regulation, centromere function and mitotic spindle formation, centrosomal function, structure and function of vault particles, telomere dynamics, trafficking of endosomal vesicles, apoptosis, and necrosis.

PARP cleavage has been reported as an apoptosis or necrosis marker in other cell types, depending on the type of cleavage. This molecule also has been reported in testicular germ line maintenance and its development; however, reports of PARP's presence on ejaculated sperm have not been established.

Our recent study conclusively establishes the presence of PARP-1 (~75 kDa) and its homologues PARP-9 (~63 kDa) and PARP-2 (~60 kDa) in both mature and immature human sperm and demonstrates that sperm from infertile men has lower PARP levels.

Using peptide mass fingerprinting analysis, we confirmed the presence of PARP immunopositive proteins PARP-1, PARP-9, and PARP-2.

Among PARP homologues' many cellular functions, DNA damage detection and repair by PARP-1 and PARP-2 are the most important. DNA fragmentation is higher in infertility patients and in immature sperm, corresponding with the low PARP levels we observed in mature sperm of infertile patients compared with levels observed in the mature sperm of donors. These findings lead to speculation that the reduced levels of PARP homologues in mature sperm might be responsible for the ineffective protection against and repair of post-testicular sperm lesions.

PARP-2 may have a role in prevention of oxygen species/oxidative stress and chemical (staurosporine)-induced sperm cell apoptosis. The presence of the PARP homologue PARP-1 (~75 kDa) suggests its role in preventing damage of mature sperm.

Additionally, we documented low levels of PARP-1, -2, and -9 in the immature sperm fractions of both donors and infertile males, suggesting a potential role for these homologues during sperm maturation.

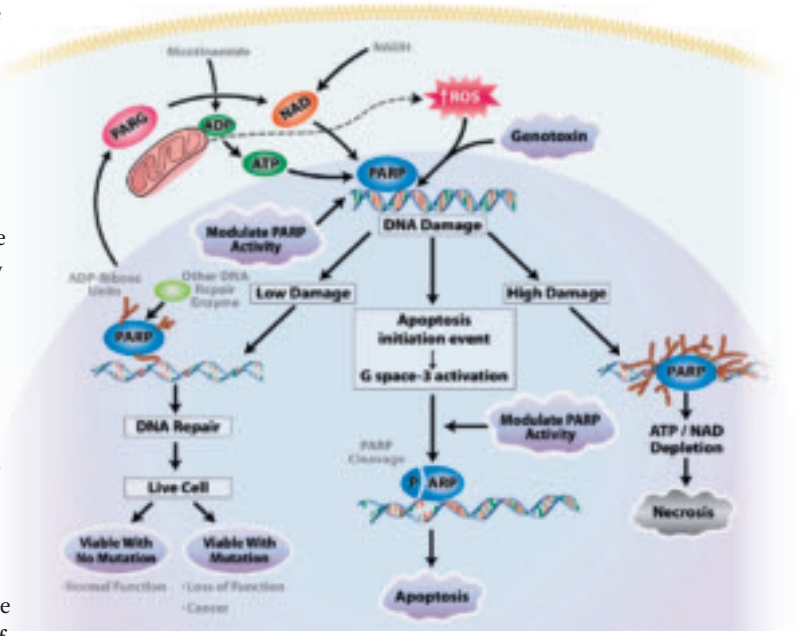
PARPs appear to have an active role in sperm cell physiology in preventing apoptosis and cellular DNA damage. Additionally, low PARP levels negatively affect sperm maturity, and potentially male fertility. PARP-1 and PARP-2 may have a role in conferring protection to the ejaculated sperm, particularly following exposure to oxidative stress and apoptosis inductors. The role of PARP-9 is still undefined.

Additional research is needed to describe the exact role of PARP homologues in sperm physiology and to confirm a causative relationship between low PARP levels and male fertility. We will continue to explore PARP's precise role in the pathophysiology of male infertility with the ultimate goal of improving the medical management of male factor infertility and success rates for assisted reproduction technologies. ■

Key Points:

The results from our study indicate an active role for PARPs in sperm cell physiology in preventing apoptosis and cellular DNA damage. We also demonstrated that low PARP levels negatively affect sperm maturity, and consequently, may affect male fertility.

PARP-1 and PARP-2 may have a role in conferring protection to the ejaculated sperm, particularly following exposure to oxidative stress and apoptosis inductors. The role of PARP-9 remains undefined.



Possible mechanism of poly (ADP-ribose) polymerase (PARP) in cell survival or cell death. PARP together with other DNA repair enzymes can repair the DNA damage in the presence of low DNA damage and high available energy. In the case of high DNA damage (due to reactive oxygen species and lack of adequate energy) PARP can be cleaved and result in apoptosis or necrosis and eventually cell death.

PARG = Poly (ADP-ribose) glycohydrolase; ADP = Adenosine diphosphate; ATP = Adenosine tripohosphate; NAD = Nicotinamide adenine dinucleotide; NADH= Nicotinamide adenine dinucleotide reduced; ROS = Reactive oxygen species.