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RESEARCH HIGHLIGHT

Pumilio 1 control of spermatogenesis: a roadmap for future research

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In this novel paper,[1] the authors examined the role of a ubiquitously expressed testicular protein, Pumilio 1, which is a post-transcriptional regulator of spermatogenesis in the testis. The mechanism of action of this regulatory protein is based on its binding to the 3′ end of mRNAs that code for kinases that regulate the p53 protein (most prominently eight of these mRNAs), which causes a Pumilio 1 binding-mediated activation of p53, and the consequent suppression of apoptosis in spermatocytes. In Pumilio 1-mutant mice, apoptosis occurs primarily in spermatocytes, which interrupts sequential male gamete development and thus reduces the fertility of the affected mice. Additional support for this mechanism came from experiments in which p53 was inhibited in mice which subsequently showed a reduction in spermatocyte apoptosis. The data also provided further evidence regarding the mRNA regulation proposed by Keene[2] which states that the multifunctional mRNAs are not physically linked, but that each mRNA cistron carries a common sequence motif that is recognized by a shared regulator, as exemplified by Pumilio 1, and its repression of the eight p53 activators.

Overall, Pumilio 1 may be considered a master protein that directs spermatogenesis *via* germ cell production and apoptosis. This is not a direct effect, but occurs by suppressing the translation of the p53 regulator kinases, which modulate the activity of p53 necessary for optimal spermatogenetic homeostasis. In order to determine whether Pumilio 1 promotes elimination of the p53 target RNAs or inhibits their translation, the authors examined two possibilities: (i) that Pumilio 1 activates regulator kinases, when p53 activity would be low, apoptosis would not be accelerated, and spermatocyte and male germ cell numbers would remain normal; and (ii) that Pumilio 1 activates p53 kinases, spermatocyte apoptosis would increase and mature sperm numbers would be reduced, resulting in oligozoospermia. The evidence supported the first hypothesis: elevated synthesis of Pumilio 1 represses p53 activity, decreases the apoptotic process and maintains sperm homeostasis. The second hypothesis is true only when the *pumilio 1* gene is deleted.

These insights are important for our understanding of various testicular and reproductive events. For instance, is Pumilio 1 action direct or an upstream factor in the spermatogenetic and spermiogenetic phases of gamete development? In men with male factor infertility is daily sperm production subject to Pumilio 1 regulation? Is sperm development, plasma membrane remodelling in terminal spermiogenesis, as well as the formation and expression of the zona pellucida and hyaluronic acid receptors, and other sperm biomarkers,[3] under Pumilio 1 regulation? In the case of accelerated apoptosis, due to a lower level of Pumilio 1 production, would any or all spermatozoa be subject to apoptosis, or spermatocytes have DNA defects or aneuploidy, or higher histone and lower transition protein and protamine levels? Would apoptosis under these conditions be a selective phenomenon that alters the proportion of fertile spermatozoa and rescue fertility in spite of lower sperm numbers? Also of interest is the relationship between Pumilio 1-mediated apoptosis and apoptosis protection involving other elements of the system, such as Bcl-2, Bcl-xL and BAK.[4] Regarding physiological fluctuations in sperm production, it is well known in the horse and sheep that around breeding time, sperm production and testicular size increase substantially, measurable by both testicular weight and the ratio of developing male gametes to Sertoli cells. Is Pumilio 1 involved in this adaptation? Future research will have to address these issues.

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3 Huszar G, Jakab A, Sakkas D, Ozenci CC, Cayli S *et al*. Fertility testing and ICSI sperm selection by hyaluronic acid binding: clinical and genetic aspects. *Reprod Biomed Online* 2007; **14**: 650–63.
4 Cayli S, Sakkas D, Vigue L, Demir R, Huszar G. Cellular maturity and apoptosis in human sperm: Creatine kinase, caspase-3 and Bcl-xL expression in mature and diminished maturity spermatozoa. *Mol Hum Reprod* 2004; **10**: 365–72.

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