INTERACTION BETWEEN BONE MORPHOGENETIC PROTEIN 4 AND RETINOID SIGNALLING IN MOUSE SPERMATOGENESIS

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Vitamin A (retinol, or ROL) is also essential for normal spermatogenesis in the rat and mouse. Vitamin A-deficient (VAD) rodents suffer various disorders including blindness and male infertility. The molecular mechanisms leading to infertility in vitamin A deficient rodents have never been fully elucidated. Following prolonged vitamin A withdrawal the only germ cells remaining in the VAD rodent testis are stem cell spermatogonia, type A1 spermatogonia, and a few preleptotene spermatocytes. Supplementing the diet of these animals with retinoic acid (RA) alleviates all symptoms of vitamin A deficiency, with the exception of sight and spermatogenesis. It is not until VAD animals are re-administered ROL through the diet, or RA is injected in repeated high doses directly into the testis, that normal spermatogenic function is restored. Here we report an interaction, in germ cells, between the Bone Morphogenetic Protein (BMP) 4 and retinoid signalling pathways that may help explain the molecular mechanics of vitamin A deficiency. We localised BMP4 gene expression to adult germ cells, in particular spermatogonia, at both the mRNA and protein level. We generated VAD mice and found that in the absence of retinoids *in vivo*, bmp4 gene expression was significantly upregulated in the testis. We also observed that the expression of bmp4 is downregulated by retinoid treatment in germ cells isolated from vitamin A sufficient mice. Expression of bmp4 mRNA in isolated spermatogonia was more sensitive to ROL rather than RA. Our results may reflect a direct requirement for ROL by germ cells for the resumption of spermatogenesis in VAD animals that involves the regulation of BMP4 expression. Furthermore our observations suggest that retinoid signalling in germ cells is different to that observed in somatic cells, and may provide insights into the role of retinoids in spermatogenesis.

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