FIBROBLAST GROWTH FACTOR RECEPTOR-1 (FGFR-1) IS ESSENTIAL FOR SPERMIOGENESIS AND MALE FERTILITY

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SNTs (Suc-1 associated Neurotrophic Factor Targets) are FGF signalling adaptors and crucial activators of the MAP/PI3 kinase pathways via FGFRs. Screening a rat testis library identified snt-2 as a potential ODF component. ODFs are a major constituent of the sperm tail that we hypothesise play an active role in motility. Using western blot analysis I have localised Fgfr-1 to the sperm tail. As such, I propose that Fgf signalling through snt-2 is involved in sperm tail development/function. To test this hypothesis, I created transgenic mice carrying a dominant-negative variant of Fgfr-1 driven by the protamine 1 promoter (haploid specific). Breeding experiments confirmed males were fertile, although one line showed a tendency towards reduced pup numbers. This effect was strengthened by Daily Sperm Production (DSP), showing significantly reduced DSP (30%↓) compared to wt mice. Transgene expression levels were expressed up to 70 times above native mRNA levels in wt mice; however there was a concurrent up-regulation of the native receptor in transgenic mice. Cumulatively this resulted in only a 6x over-expression in transgene: native mRNA, and illustrated the presence of a feedback mechanism controlling Fgfr-1 expression. To increase transgene expression, I crossed independent lines (double heterozygous, DH) males. Breeding experiments showed males from 1 cross were significantly subfertile (2 *v.* 10 in wt mice) . DSPs were further reduced, (41%↓) compared to wt mice. Collectively this data shows Fgfr-1 signalling is required for quantitatively normal spermiogenesis, but is also likely to have a post testicular role in sperm function. I hypothesise this is mediated via activation/regulation of motility through the MAP/PI3 kinase pathways. Further, these mouse models provide compelling evidence that infertility in Kallmann's Syndrome patients is composed of both hypothalamic and testicular components. These mice will provide valuable insights into the signal transduction mechanisms controlling sperm function and avenues for contraceptive development.

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