SUMMARY

SPIN1 binds meiotic spindle and is necessary for meiotic progression in animal models. It is also a positive regulator of human ovarian cancer and a few cancer cell lines. Here, we examined functional significance and expression regulation of SPIN1, SPIN3 and SPIN4 in a human testis germ cell tumor (seminoma) TCam-2 cell line, representing male germ cells blocked at early developmental stage. We show, for the first time, that SPIN3 and SPIN4 paralogues, have differential effects, as compared to SPIN1. Namely, while overexpression of SPIN1 caused a significant increase of proliferation, overexpression of SPIN3 and SPIN4 elicited its decrease. Also, opposite to SPIN1 decreasing apoptosis, overexpression of SPIN3 and SPIN4 induced it. Thus, it seems that SPIN1 is oncogenic whereas SPIN3 and SPIN4 are anti-oncogenic in TCam-2 cells. However, both SPIN1 and SPIN3 stimulated the cell cycle, while SPIN4 did not. In addition, using luciferase reporters carrying *SPIN* 3'untranslated regions (3'UTR) and measuring endogenous *SPIN* expression, we show for the first time that *SPINs* are strongly targeted by PUM1 and PUM2 for repression. Addressing other SPIN regulators and PUM effectors may shed light on differential function of paralogues and mechanism of PUM role in germ cells and seminoma. Given previously reported cooperation of Pum with Nanos protein, in the context of germ cell development, as well as reports about the role of Nanos in apoptosis downregulation in *Drosophila* germ cells, NANOS1, NANOS2 and NANOS3 human homologues were studied to test whether they posttranscriptionally regulated *SPINs*. Indeed, it was shown here that *SPINs* are regulated by NANOS paralogues and that the regulation pattern is particular for each NANOS/3'UTR-*SPIN* combination. Interestingly, exclusively NANOS1 had an anti-apoptotic influence on TCam-2 cells while NANOS2 and NANOS3 were neutral. Moreover, it was found here that *NANOS1* p.P34TS78del mutation, previously identified in association with lack of germ cells in testes, caused NANOS1 to functionally switch from being anti-apoptotic towards pro-apoptotic. The mutated NANOS1 triggered this switch by disrupting repression of pro-apoptotic SPIN3 mRNA while enhancing repression of anti-apoptotic SPIN1, leading altogether to apoptosis increase and proliferation decrease of TCam-2. Such mechanism may underlie lack of germ cells in patients carrying NANOS1 mutations. This work underscores conservation of Nanos from flies to humans, as a repressor of apoptosis-related mRNAs in germ cells.