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Award Winners

A-9

Suppression of transforming growth factor-beta signaling enhances spermatogonial proliferation and spermatogenesis recovery following chemotherapy

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Background: Spermatogonial stem cells hold great promise for fertility preservation in prepubertal boys diagnosed with cancer. However, the low number of Spermatogonial stem cells limits their clinical applications. Could small molecules (SM) are chemically synthesized molecules that diffuse across the cell membrane to specifically target proteins involved in signaling pathways, and studies have reported their ability to increase the proliferation or differentiation of germ cells.

Objective: SM which target (or modify) signaling pathways lead to increased proliferation of undifferentiated spermatogonia following chemotherapy?

Materials and Methods: In our experimental study, spermatogonia were collected from four brain-dead individuals and used for SM screening in vitro. For in vivo assessments, busulfan-treated mice were treated with the selected SM (or vehicle, the control) and assayed after 2 (three mice per group) and 5 weeks (two mice per group). We investigated the effect of six SM on the proliferation of human undifferentiated spermatogonia in vitro using a top-bottom approach for screening. We used histological, hormonal and gene-expression analyses to assess the effect of selected SM on mouse spermatogenesis. All experiments were performed at least in triplicate and were statistically evaluated by Student's t-test and/or one-way ANOVA followed by Scheffe's or Tukey's post-hoc.

Results: We found that administration of SB431542, as a specific inhibitor of the TGFb1 receptor (TGFbR1), leads to a two-fold increase in mouse and human undifferentiated spermatogonia proliferation. Furthermore, injection of SB to busulfan-treated mice accelerated spermatogenesis recovery as revealed by increased testicular size, weight and serum level of inhibin B. Moreover, SB administration accelerated both the onset and completion of spermatogenesis. We demonstrated that SB promotes proliferation in testicular tissue by regulating the cyclin-dependent kinase inhibitors 4Ebp1 and P57 (proliferation inhibitor genes) and up-regulating Cdc25a and Cdk4 (cell cycle promoting genes).

Conclusion: This is the first study to report acceleration of spermatogenesis recovery following chemotherapy by administration of a single SM. Our findings suggest that SB is a promising SM and should be assessed in future clinical trials for preservation of fertility in men diagnosed with cancer or in certain infertility cases (e.g. oligospermia).

Key words: *Spermatogonial stem cells, Small molecules, Fertility preservation.*

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