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High temperature suppressed SSC self-renewal through S phase cell cycle arrest but not apoptosis

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Abstract

Background: High temperature has a very adverse effect on mammalian spermatogenesis and eventually leads to sub- or infertility through either apoptosis or DNA damage. However, the direct effects of heat stress on the development of spermatogonial stem cells (SSCs) are still unknown because SSCs are rare in the testes.

Methods: In the present study, we first used in vitro-cultured SSCs to study the effect of heat shock treatment on SSC development. Then, we used RNA-Seq analysis to identify new genes or signalling pathways implicated in the heat stress response.

Results: We found that 45 min of 43 °C heat shock treatment significantly inhibited the proliferation of SSCs 2 h after treatment but did not lead to apoptosis. In total, 17,822 genes were identified by RNA-Seq after SSC heat shock treatment. Among these genes, we found that 200 of them had significantly changed expression, with 173 upregulated and 27 downregulated genes. The number of differentially expressed genes in environmental information processing pathways was 37, which was the largest number. We screened the candidate JAK-STAT signalling pathway on the basis of inhibition of cell cycle progression and found that the JAK-STAT pathway was inhibited after heat shock treatment. The flow cytometry results further confirmed that heat stress caused S phase cycle arrest of SSCs.

Conclusion: Our results showed that heat shock treatment at 43 °C for 45 min significantly inhibited SSC self-renewal through S phase cell cycle arrest but not apoptosis.

Keywords: High temperature, SSCs, Self-renewal, Cell cycle arrest, Apoptosis

Background

Spermatogenesis is a process by which spermatogonial stem cells (SSCs) self-renew and differentiate into sperm. Any error during spermatogenesis results in male infertility. Infertility occurs in 10–15% of all couples, and male factors account for 50% of cases. High temperature is one of the causes of male infertility [1]. Cryptorchidism or increased scrotal temperature leads to nonobstructive azoospermia or asthenozoospermia.

The scrotum is generally 2–7 °C cooler than the core body temperature in most male mammals, and the temperature of the testes is tightly regulated by a heat exchange system [2]. If the testes fail to descend into the scrotum during postnatal development, they are exposed to elevated temperature (the core body temperature) and lose germ cells [3]. Male germ cells (especially haploid spermatids) are significantly reduced or completely lost in the cryptorchid testes [4]. The transition of gonocytes into type A dark spermatogonia (SSCs) in cryptorchid testes is impaired [5]. Thus, the thermoregulation of the testes is essential for spermatogenesis. The reason why most mammals have evolved to maintain their testes at low temperatures remains unclear [6].

Scrotal high temperatures led to the interruption of spermatogenesis and reductions in sperm quality and

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