Discovery of an atypical heat shock factor, HSF5, involved in meiotic mechanisms has implications for male infertility

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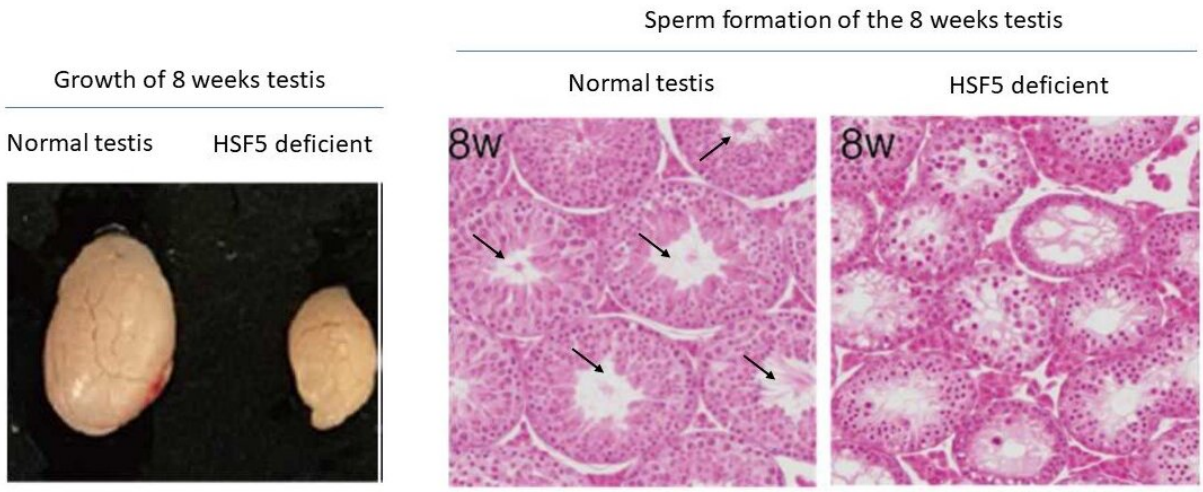


Deletion of *hsf5* in mice results in the impaired development of testis (left), and the absence of spermatids and spermatozoa (right), which leads to the failure of sperm formation. Credit: Kei-ichiro Ishiguro, Kumamoto University

Kumamoto University researchers have identified a novel heat shock factor (HSF), designated as HSF5, which plays a crucial role in the

completion of meiosis and the activation of genes essential for sperm formation. This discovery provides valuable insights into underlying causes of spermatogenic failure, the major contributor to male infertility.

Furthermore, unlike other typical heat shock factors, which primarily regulate gene expression in response to stress, such as heat shock, HSF5 plays a specific role in male germ production during meiosis under non-stress conditions.

In eukaryotic cell division, genomic information is equally distributed to daughter cells during mitosis, whereas it is halved during a specialized type of cell division called meiosis, which is necessary for germ cell production. In male germ cell, sperm formation follows the completion of meiosis, with multiple gene regulatory programs.

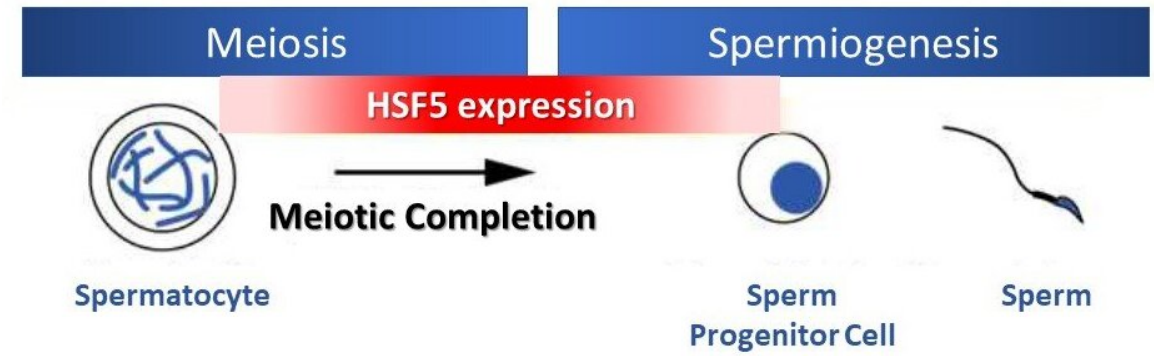
However, the mechanisms governing meiotic progression and the specific transcription factors involved remain poorly understood, posing significant challenges in reproductive medicine, particularly concerning male infertility.

To address these gaps, Professor Kei-ichiro Ishiguro, Assistant Professor Ryuki Shimada, and their research team aim to clarify the mechanisms regulating male meiosis that lead to sperm production, focusing on the identification and characterizing related transcription factors. The paper is published in the journal *Nature Communications*.

In a previous study, the team identified a meiosis switch gene MEIOSIN, which activates the expression of hundreds of genes involved in sperm formation. Among these genes, heat shock factor emerged as a focus of interest testes due to the testes' sensitivity to heat stress, given their external positioning, which maintains a temperature of 3–4 degrees Celsius lower than the body's internal temperature of 37 degrees Celsius.

Although the main roles of heat shock factors such as HSF1, HSF2, HSF3, and HSF4 have been well identified, the function of HSF5 remains unclear.

"Whether HSF5 shares similar functions with other heat shock factors, or exhibits entirely different functions poses an intriguing question, and addressing this question was the original intention of our study," explains Professor Ishiguro.



HSF5 is required for spermatocytes to progress beyond the substage of meiotic prophase during spermiogenesis under non-stress conditions. Credit: Kei-ichiro Ishiguro, Kumamoto University

Surprisingly, different from other HSFs responding to stress, the study showed that HSF5 plays an essential role in the meiotic prophase

progression in male germ cells under non-stress conditions. HSF5 is required for progression beyond the pachytene stage during spermatogenesis, guiding the meiotic program towards completion and activating genes associated with sperm formation.

Just like other transcription factors, HSF5 binds to DNA promoters to regulate gene expression. What distinguishes HSF5 is its unique target specificity. The research revealed that the DNA motif it recognizes for binding to gene promoter, differs from those bound by other canonical HSF family transcription factors.

All these findings underscore HSF5's atypical role in gene expression during meiotic prophase in males.

The results of this study were validated through experimentation on mice, with a crucial recognition that HSF5 is also present in humans. Given that many underlying causes of infertility in humans, especially in cases of spermatogenic failure, remain elusive, the findings of this study are anticipated to contribute significantly to understanding the pathogenesis of male infertility.

More information: Saori Yoshimura et al, Atypical heat shock transcription factor HSF5 is critical for male meiotic prophase under non-stress conditions, *Nature Communications* (2024). DOI: 10.1038/s41467-024-47601-0

Provided by Kumamoto University

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