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Research Progress on Male Sterility in Dzo (Yak-Cattle Hybrid)

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Abstract Male dzo from the F1 to F3 generations are sterile, which impedes the utilization of hybrid vigor in dzo and constrains the development of plateau animal husbandry in China. The underlying mechanism of this phenomenon has long been a focal point in yak crossbreeding improvement research. This review summarizes the mechanisms underlying male sterility in dzo from histological, physiological, and multi-omics perspectives, providing research directions for further exploration of the mechanisms of male sterility in dzo.

Key words Dzo, Testis, Male sterility, Multi-omics sequencing

0 Introduction

The yak (*Bos grunniens*) is an important primitive domestic animal in China, primarily distributed in alpine pastoral areas above 3 000 m on the Qinghai - Tibet Plateau, and is renowned as the "ship of the plateau". It holds an irreplaceable position in economic, social, and cultural spheres and is acclaimed as an "all-purpose livestock"[1]. However, yaks exhibit relatively low milk and meat production performance. Although their hybrid offspring with common cattle (*Bos taurus*), known as dzo, exhibit significant hybrid vigor, the female hybrids (female dzo) are fertile, whereas the male hybrids (male dzo) from the F1 to F3 generations are sterile. This prevents the fixation of hybrid vigor through intercrossing[2], which not only limits the utilization of dzo genetic resources but also constrains the development of its industry chain, making it a subject worthy of in-depth research. In recent years, with the advancement of interdisciplinary research involving molecular biology, genetics, and reproductive physiology, significant breakthroughs have been made in understanding the mechanisms of male sterility in dzo. This article aims to provide technical references for elucidating the mechanisms of male sterility in dzo and to offer research perspectives for yak crossbreeding improvement.

1 Morphological and structural characteristics of the testis

Male dzo and yaks share a fundamentally similar composition of reproductive organs, including testes, epididymides, ductus deferentes, scrotum, and penis. However, significant developmental differences exist, with dzo testes being lighter in weight[3]. The testes and epididymides of F1 dzo are underdeveloped, exhibiting a narrow scrotum, thickened tunica albuginea, sparse vasculature, soft texture, and a deep yellow cut surface[4-5]. As the backcross generation increases, these anatomical characteristics progressively approximate those of yaks. By the F3 generation, the morphology of the tunica albuginea and the color of the cut surface become largely consistent with those of male yak testes[3]. In F1 dzo, the seminiferous tubules are fewer in number and disorganized, hindering spermatogenic cell development. The seminiferous epithelium is only 1 - 2 layers thick, consisting mainly of Sertoli cells and very few spermatogonia and spermatocytes, with no spermatozoa produced. Furthermore, Leydig cells are sparse and functionally impaired, leading to insufficient hormone levels. Spermatogenic function gradually recovers with increasing backcross generations. In F2 dzo, the seminiferous epithelium thickens to 3 - 4 layers, and round spermatids appear. F3 dzo show multiple layers of spermatogenic cells and spermatozoa at various developmental stages, with interstitial tissue closely associated with the seminiferous tubules. Spermatogenic function is largely restored by the F4 generation, but hybrid vigor is concomitantly lost[6-7]. Studies indicate individual variation within the same generation; spermatogenesis can be observed in some F3 dzo, whereas it is essentially arrested in F1 to F2 dzo. Additionally, the diameter of dzo germ cells is significantly smaller than that of the parental species.

2 Specificity of chromosomal meiosis and recombination

The degree of hybrid sterility is closely related to the genetic distance between the parental species. Differences in chromosome number, morphology, and structure are key factors contributing to sterility. Yak and cattle belong to interspecific hybridization within the same genus. Dzo share the same chromosome number ($n = 30$) and G-band, C-band, and silver-stained nucleolar organizer region characteristics as their parents. Autosomes are all telocentric, and the X chromosome is submetacentric[8]. Howev-

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er, significant differences exist in the relative lengths of parental autosomes, and the morphology of the Y chromosome is markedly distinct (cattle Y chromosome is metacentric, whereas yak and dzo Y chromosomes are submetacentric). This leads to abnormal chromosome synapsis in spermatocytes during spermatogenesis in F1 dzo, disruption of the balance between X and Y chromosomes, and impaired formation of the synaptonemal complex (SC), thereby causing reproductive isolation-based sterility[9]. Cytological observations further reveal that SCs in F1 dzo frequently exhibit nodules, tangles, breaks, or even disintegration, resulting in only a small number of abnormal spermatozoa; in F2 dzo, the number of cells capable of forming SCs increases, and their morphology improves; in F3 dzo, the majority of spermatocytes can form essentially normal SCs, although phenomena such as chromosome breaks and unbalanced segregation persist in some instances, the sex chromosome SC often appears linear, with occasional tangles, and this generation represents a critical period for fertility restoration; it is not until the F4 generation that the majority of individuals become fertile[10-11]. These results demonstrate that abnormalities in synaptonemal complex formation, arising from chromosomal structural differences, constitute a crucial cytogenetic mechanism for male sterility in dzo.

3 Hormonal expression differences

Spermatogenesis is a hormonally regulated process, primarily governed by the hypothalamic-pituitary-gonadal (HPG) axis: Gonadotropin-releasing hormone (GnRH) secreted by the hypothalamus stimulates pituitary basophilic cells to secrete follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which subsequently regulate testosterone (T) synthesis and spermatogenesis[4]. Studies have found a significant reduction in basophilic cells within the anterior pituitary of F1 and F2 male dzo, with the number of FSH-producing cells being only 20% -30% of that in the parental species, leading to insufficient FSH secretion. This directly impairs seminiferous tubule development and causes blockage of spermatogenic epithelium formation[12-13]. Although LH secretion is normal in F1 dzo, Leydig cells develop well, and testosterone levels do not significantly differ from those in yaks, allowing them to retain normal male characteristics and sexual behavior, spermatogenesis nevertheless fails to complete[14-15]. Further research indicates that androgen receptor (AR) expression in Leydig cells of dzo testes is reduced, while the expression of 3β-hydroxysteroid dehydrogenase (3β-HSD), a key enzyme in testosterone synthesis, is enhanced. As the AR signaling pathway is essential for spermatogenesis, its functional impairment may hinder the normal progression of spermatogenesis[16]. It is evident that male sterility in dzo is not only associated with dysregulation of gonadotropin secretion but also involves impaired local hormonal response within the testis. In-depth analysis of its regulatory mechanisms at the hormonal level holds promise as a crucial breakthrough for addressing the sterility issue.

4 Multi-omics analysis of regulatory mechanisms in dzo male sterility

In recent years, the rapid development of omics technologies, including genomics, transcriptomics, proteomics, and epigenetics, has provided novel perspectives for deciphering the molecular mechanisms underlying male sterility in dzo. Genomics and Structural Variation (SV): Significant structural variations (SVs), including deletions, duplications, and inversions, exist between yak and common cattle genomes[5]. Studies found that approximately 27.78% of differentially expressed genes (DEGs) in dzo testicular tissue harbor SV sites. These variations may directly cause abnormal germ cell development in dzo by altering gene expression or interfering with meiotic recombination[17]. X-chromosome-linked genes exhibit aberrantly high expression during meiosis in dzo, potentially related to failure of meiotic sex chromosome inactivation (MSCI). Comparative proteomics: Proteomic studies revealed that proteins associated with energy metabolism (*e. g.*, LDHB), chromosome recombination (*e. g.*, RAD51), and spermiogenesis (*e. g.*, TSSK6, TPPP2) are expressed at significantly lower levels in dzo testes compared to yak testes, while oxidative stress-related proteins (*e. g.*, SOD2) are significantly upregulated. This suggests that energy metabolism imbalance and oxidative damage may synergistically contribute to spermatogenic failure[2]. Epigenetic regulation plays a significant role in dzo sterility[1]. Studies found that histone modification levels (*e. g.*, H3K27me3) are significantly lower in dzo Sertoli cells compared to yak Sertoli cells[18-19], potentially interfering with the transformation of gonocytes into spermatogonia by affecting chromatin accessibility[5]. Furthermore, long non-coding RNA (lncRNA) analysis in epididymal tissue identified 18 859 differentially expressed lncRNAs. Some of these lncRNAs (*e. g.*, LNC_000432) participate in the formation of sperm functional defects by targeting and regulating sperm maturation-related genes such as TNP1 and PRM2[8].

5 Conclusions

Male sterility in dzo is a complex biological phenomenon involving multiple levels, including the morphology and structure of the reproductive system, cytogenetics, hormonal secretion, and molecular regulation. With the deepening of multidisciplinary research, the mechanisms underlying dzo male sterility are gradually being unveiled, yet many questions remain unresolved. Future research should focus on the following key areas: Molecular mechanisms: In-depth investigation of key genes and signaling pathways associated with spermatogenesis in dzo testes. Epigenetic regulation: Exploration of the roles of DNA methylation and histone modifications in dzo spermatogenesis. Breeding technologies: Utilization of gene editing techniques (*e. g.*, CRISPR/Cas9) to improve the reproductive performance of dzo. Production applica-

tion: Integration of molecular breeding with traditional breeding techniques to develop new dzo varieties possessing both hybrid vigor and fertility. Through multidisciplinary collaboration and the application of new technologies, it is anticipated that the bottleneck of male sterility in dzo can be overcome, thereby promoting the sustainable development of yak crossbreeding improvement and its associated industry chain.

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