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HUWE1 and Its Role in Gametogenesis: A Critical Regulatory Nexus

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Abstract

HUWE1 is an Ubiquitin ligase found in the HECT domain involved in spermatogenesis, many other cellular processes. The current study aims to elucidate the function of HUWE1 in the processes of oogenesis and spermatogenesis. In males, it controls sperm development and meiosis, while in females, the enzyme is responsible for oocyte maturation, meiosis, and embryo development. It is located in ovaries and testis in both females and males respectively. The vital role was validated by different animal model studies on mice through knockout and knockdown of HUWE1. These findings indicated that the deletion of HUWE1 resulted in infertility in both sexes, thereby proving its significance in gametogenesis. Based on the findings, it is concluded that, that deletion or dysfunction of HUWE1 could lead to defective spermatogenesis and oogenesis, resulting in infertility.

Keywords: Spermatogenesis, Oogenesis, HUWE1, infertility, animal models

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1. INTRODUCTION

1.1. Background on Human Fertility and Gametogenesis

Sperm cell, embryo development, and sexual maturity depend on adequate hormone regulation in both the male and female reproductive systems (Kirillova et al., 2021). The molecular gatekeeper as HUWE1, controls reproductive proteins, highlighting the importance of a detailed knowledge of their functions and mechanisms (Qi et al., 2022). Gametogenesis, the process by which eggs and sperm are created, is brought about through meiosis. Since there are two cell divisions, meiosis produces gametes that have a portion of the parent cell's chromosome count (EMAN et al., n.d.). Both pairs of chromosomes in the nucleus are split in the first division, and the chromatids that were created earlier in the cell's life cycle are split in the second. Oogenesis is the process that produces eggs, and spermatogenesis is the process that produces sperm (Lu et al., 2023).

1.1.1. Oogenesis

The exterior sections of the ovaries are where oogenesis is carried out. Comparable to the formation of sperm, oogenesis starts with a germ cell recognized as an oogonium (plural: oogonia) (Zhai et al., 2023). However, this cell continues through mitosis to proliferate, ultimately generating an embryo with one to two million cells (Zhai et al., 2023). A key oocyte is the cell that initiates meiosis. The initial division of meiosis will commence in this cell, but it will be hindered at the very first prophase stage. Many upcoming eggs are in the prophase phase when they are born (Wasielak-Politowska & Kordowitzki, 2022). Due to anterior pituitary hormones, a large number of ovarian follicles develop during adolescence. As a result, the initial oocyte completes the first meiotic division. One cell, referred to as a secondary oocyte, receives the majority of the cell's organelles and cellular parts when the cell splits unevenly, while the other cell receives only a small amount of cytoplasm and one pair of chromosomes (Phelan, 2023). This second cell, called a polar body, usually dies. A second meiotic arrest occurs at the metaphase II stage. Following ovulation, this second oocyte will be released and travel through the oviduct to reach the uterus. When the secondary oocyte is fertilized, the cell undergoes meiosis II, completes meiosis, produces a second polar body, and produces a fertilized egg containing. Once a secondary oocyte is fertilized, the cell undergoes meiosis II, finishes meiosis, generates a second polar body, and produces a fertilized egg that has all 46 of a human's chromosomes, 50% of which originate from the sperm (Ma et al., 2023).

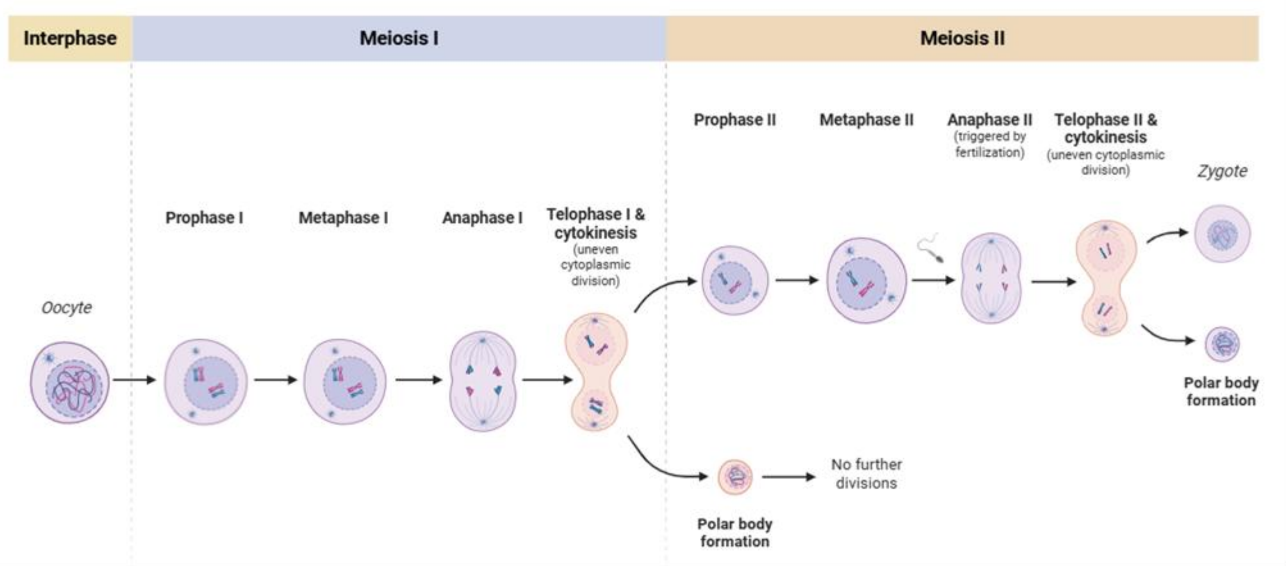

Figure 1. Exhibits the stages of oogenesis

1.1.2. Spermatogenesis

The method by which male germ cells, termed spermatogonia, evolve into completely developed spermatozoa, or sperm, is called spermatogenesis (Waqas, 2021). The mitosis of spermatogonia, the meiotic development of spermatocytes, and the morphological conversion of spermatids becoming spermatozoa are the three primary steps of this process, which takes place inside the seminiferous tubules (Houda et al., 2021). The germ cells travel inside the seminiferous epithelium during spermatogenesis, which causes the connections between Sertoli cells with sperm cells, along with those between Sertoli cells at the blood-testis barrier (BTB) to be reorganized (Luaces et al., 2023). Mature sperm will be emitted from the basal part of the seminiferous epithelium towards the seminiferous tubule lumen following the completion of spermatogenesis. Furthermore, spermatogenesis failed as evidenced by the early loss of germ cells by Sertoli cells (Houda et al., 2021). Sertoli cells are essential for spermatogenesis because they give sperm cells a specific environment. The proper maturation and transportation of mature spermatozoa are facilitated by these cells, which also help to maintain the BTB (O'Donnell et al., 2022). It is important to comprehend the complex processes of spermatogenesis to identify the reasons behind male infertility and create viable treatment plans.

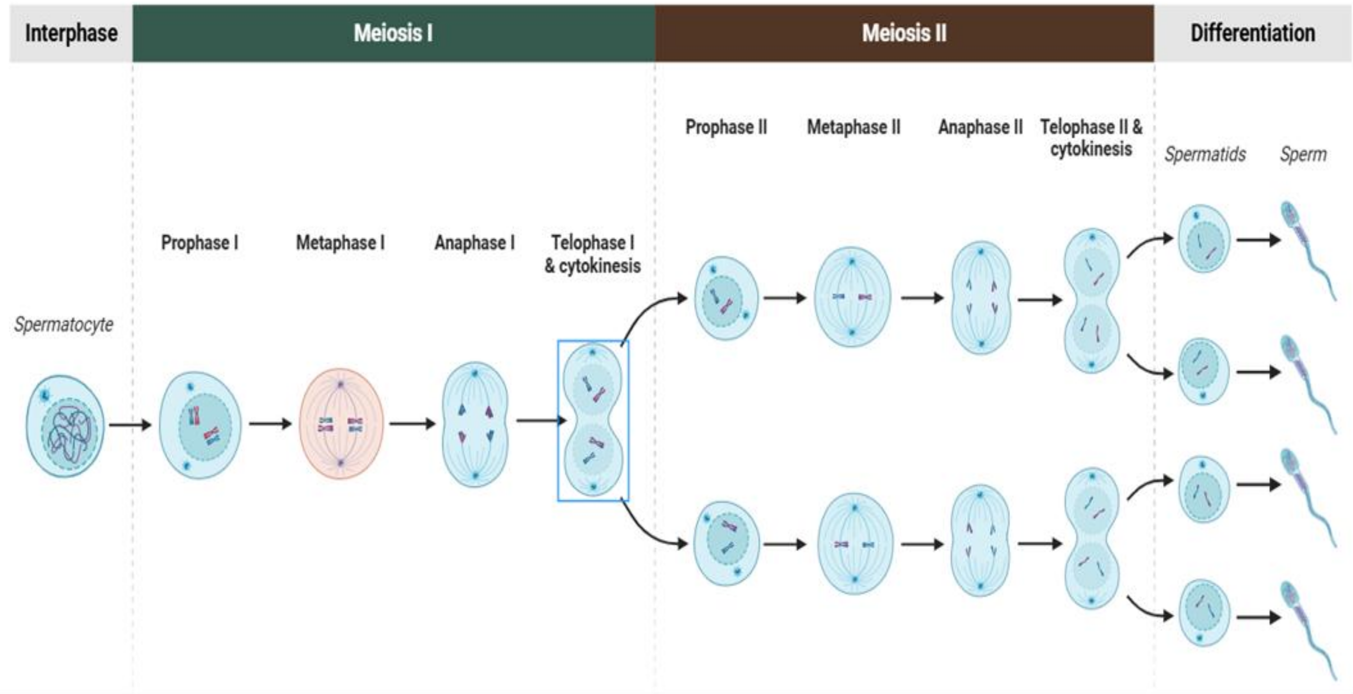

Figure 2. Depicts the stages of spermatogenesis.

1.2. Ubiquitin-Proteasome System (UPS) Role in Germ Cell Regulation

A modification known as ubiquitination, which has been constant throughout evolution, occurs when ubiquitin is attached to the residues of substrate eukaryotic cells (Kelsall, 2022). E1 as ubiquitin-activating enzymes, E2: ubiquitin-conjugating enzymes, and E3: ubiquitin ligases are the three chief enzymes that facilitate the ubiquitination process. RING-type E3 ligases mediate straight ubiquitin transfer from enzymes to their substrate. HECT-type and RBR-type E3 ligases shift the ubiquitin moiety from the E2-enzyme to a catalytic cysteine within the E3 enzyme initially, followed by the substrate. (Yang et al., 2021). Many physiological functions, including signal transduction, cell division, differentiation, and death, are regulated by ubiquitination and rely on the kind of polyubiquitin chain (Damgaard, 2021). Protease-mediated proteolysis of the substrate has been related to K11 and K48-linked polyubiquitin chains (Luo, 2024). Innate immune responses and signalling are mediated by polyubiquitin chains that are K63- along with M1-linked (Huang et al., 2022).

1.3. HUWE- an Ubiquitin E3 ligase

A broad class of enzymes known as E3 ubiquitin ligases forms a three-enzyme ubiquitination cycle with the ubiquitin-activating enzyme E1 and the ubiquitin-conjugating enzyme E2. (Yang et al., 2021). The ubiquitination pathway and the transport of ubiquitin protein to the lysine sites of target substrates are mediated by E3 ubiquitin ligases (Toma-Fukai & Shimizu, 2021). The significant E3 ligase HUWE1 is required for the growth of cells, apoptosis, and stress responses. HUWE1 influences spermatogenesis, cancer, signalling pathways, transcriptional regulation, neurological differentiation, DNA damage responses, & more (Qi et al., 2022). Additionally, the X chromosome contains the Huwe1 gene, which is connected to intellectual disability linked to the X chromosome (Santos-Rebouças et al., 2023). The present review discussed the role of HUWE1 in male gametogenesis.

2. Structure and function of HUWE1

2.1. Domain Organization

HECT, UBA, as well as WWE domain-comprising protein 1 (HUWE1), is a big E3-ligase with a length of 4374 aa (humans) and 4378 aa (mice) (Sun, Chen, et al., 2023). Five different groups identified and examined full-length cDNA in 2005 after HUWE1 was first discovered in the study of big cDNA clones from the brain (Wen, 2021). The human and mouse HUWE1 protein sequences are over 90% identical (Qi et al., 2022). Human HUWE1 has a C-terminal HECT ubiquitin ligase domain and all four N-terminal armadillo repeat-like domains (ARLD1-4) (Zhou et al., 2023) (Figure 3) (Kao et al., 2018). A domain, UBA, and WWE domain that participates in proteolysis, while the BH3 domain regulates protein-protein interactions (Müller, 2023).

Significant progress has been made in recent years in understanding the substrate-specificity of the HUWE1 protein and its oversight of HECT ligase activity (Sun, Tian, et al., 2023). The HUWE1 size has been shown to regulate the ubiquitination of many different substrates via its massive, highly active substrate-binding ring (Grabarczyk et al., 2021).

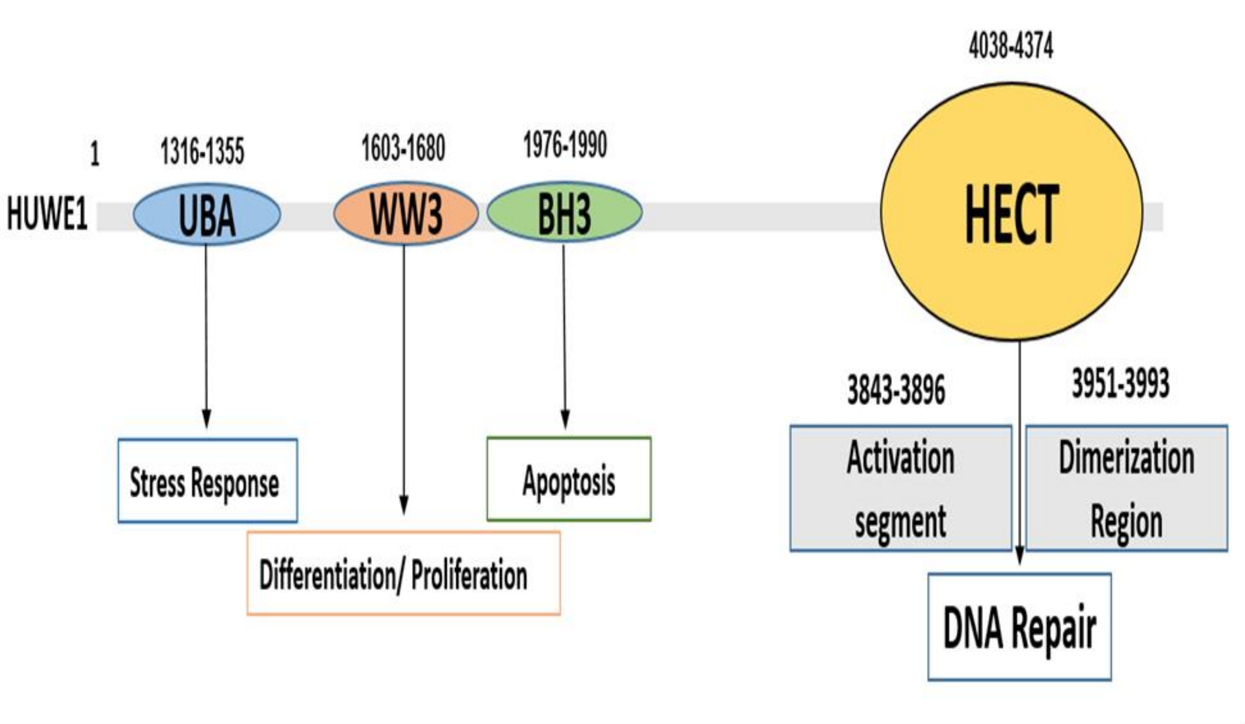

Figure 3. Depicts the domain organization of HUWE1.

2.2. Substrate Specificity of HUWE1

The HUWE1 is believed to regulate more than 40 substrates (Yang et al., 2021). This revealed that HUWE1 activity is regulated by a conformational transition. The creation of activity inhibitors with substrate-selective recruitment will be greatly aided by structural characterization of the HUWE1 protein, which has emerged as an appealing and promising therapeutic target for the treatment of cancer and other illnesses (Gavali et al., 2021). HECT domains are potentially druggable, and bicyclic peptides, as well as ubiquitin variations, have been shown to effectively and specifically limit HECT ligase activity (LaPlante & Zhang, 2021).

Table 1. The table lists known substrates of HUWE1, along with their alternative gene names and the type of ubiquitination (Qi et al., 2022).

Substrates	Alternative gene name	Ubiquitination-type
Cdc6	HUWE1	Polyubiquitination
Mcl-1	Mule	K48-associated polyubiquitination
H2AX	HUWE1	K48-associated polyubiquitination
PCNA	HUWE1	Only interaction
histone H1	HUWE1	mono-ubiquitination
Myst2	HUWE1	ubiquitination
Pol β	Mule	Polyubiquitination
Pol λ	Mule	Polyubiquitination
Chk1	HUWE1	Polyubiquitination
DDIT4	HUWE1	Polyubiquitination
Gadd45b	HUWE1	Polyubiquitination
DNA-PKcs	HUWE1	Neddylation
MYC	HectH9	K63-associated polyubiquitination
c-Myc	HUWE1	Polyubiquitination

p53	UREB1	K48-linked polyubiquitination
p53	ARF-BP1-tumor cells	Polyubiquitination
c-Myc and Miz	HUWE1	K48-linked polyubiquitination
TopBP1	HectH9	Polyubiquitination
HDAC2	Mule	Polyubiquitination
H1.3	HUWE1	Polyubiquitination
CTCF	ARF-BP1	K48-linked polyubiquitination
Dvl	HUWE1	K63-linked polyubiquitination
MyoD	HUWE1	Polyubiquitination
BRCA1	HUWE1	Polyubiquitination
TIAM1	HUWE1	Polyubiquitination
EGFR	HUWE1	Polyubiquitination
IKK2	HectH9	K63-associated polyubiquitination
HIF-1α	HUWE1	Polyubiquitination
HAUSP	HectH9	K63-associated polyubiquitination
MEN2	HUWE1	Polyubiquitination
WIPI2	HUWE1	Polyubiquitination
Ubl4A	HUWE1	Polyubiquitination
Histones (H1, H2A, H2B, H3, and H4)	E3 Histone	Polyubiquitination
Ascl1	HUWE1	Polyubiquitination
Atoh1	HUWE1	Polyubiquitination
N-Myc	HUWE1	Polyubiquitination
TRAF6	HUWE1	K48-K63 branched ubiquitination
Miz1	HUWE1	K48-associated polyubiquitination
p65	HUWE1	Polyubiquitination
NLRP3	HUWE1	K27-linked polyubiquitination
AIM2	HUWE1	K27-linked polyubiquitination
NLRC4	HUWE1	K27-associated polyubiquitination
Ets-1	HUWE1	Polyubiquitination

2.3. Function ubiquitination and proteasome degradation

Several enzymatic processes resulting in the ubiquitination of proteins and their subsequent destruction or modification comprise the ubiquitin proteasome system as UPS (Li et al., 2022). Human infertility has been linked to changes in UPS genes, indicating that UPS plays a part in gametogenesis (spermatogenesis and oogenesis) (Fang et al., 2022). The current review discussed and analyzed the significant role of HUWE1 in spermatogenesis.

3. Localization and Expression of HUWE1

An essential part of testicular growth and sperm development (spermatogenesis) is performed by HUWE1, a kind of E3 ubiquitin ligase enzyme (Xiong et al., 2022). Early in the development of germ cells, HUWE1 is found to be highly active, particularly in spermatogonia as well as pachytene spermatocytes. It is significant because of its distinct pattern of localization; in testis cells, HUWE1 is primarily present in the nucleus, unlike other tissues where it is primarily found in the cytoplasm (Berruti, 2021). The protein is mainly expressed in the testis within the seminiferous epithelium. It also suggests that it might have specific roles in controlling chromatin restructuring and gene expression during spermatogenesis (Wang et al., 2022). Studies on rats and mice demonstrated its crucial importance, showing that sperm cells lacking HUWE1 cannot grow properly and may experience DNA damage (Cruz Walma et al., 2022). The above data suggest that HUWE1 is more than just another cellular protein; it is a crucial mediator that ensures the healthy development of male sperm cells and fertility. It is located primarily on the X-chromosome and is mainly involved in the reproductive process, such as meiosis, and embryo development (Xu et al., 2024).

4. Mechanism and Function of HUWE1-(Gametogenesis)

4.1. HUWE1 Involved in Cell Cycle Regulation

The p27-Kip1, along with other CDK inhibitors that block cell division, is targeted by HUWE1 (Bencivenga et al., 2022). By degrading cyclin-dependent kinase (CDK) inhibitors, HUWE1 facilitates cell cycle entry and development, specifically throughout the mitotic to meiotic phases of germ cell development (Lin & Jin, 2023).

4.2. Management of Apoptosis and Sperm Cells

HUWE1 primarily targets the tumor suppressor receptor p53, which responds to DNA damage by triggering cell death (Shan et al., 2024). It supports the elimination of abnormal sperm cells by tagging them with ubiquitin. This mechanism prevents excessive germ cell death while enabling the eradication of damaged or defective cells (Berruti, 2021).

4.3. Management of Spermatogonial Stem Cells

For sperm to maintain lifelong spermatogenesis, HUWE1 is crucial for controlling the self-renewal and differentiation of spermatogonial stem cells and their subsequent development (Tan et al., n.d.). It consists of Wnt signaling, Notch signaling, as well as the Akt/PIK3 pathway. HUWE1 indirectly regulates this development and reproductive pathway by changing upstream inhibitors such as PTEN or Akt phosphorylation levels. Akt/PIK3 is involved in SSC survival and sustained function under stress. Since Notch dysregulation could cause unchecked proliferation or SSC depletion, and excessive activation may result in defects in SSC differentiation, HUWE1 facilitates proper stem cell function.(Yuan et al., 2022).

4.4. Genome Stability

During meiosis, germ cells undergo DNA double-strand breaks, also termed DSBs, to promote recombination. (Qu et al., 2021). By its regulation of proteins associated with DSB repair processes, including those connected to homologous recombination, HUWE1 supports the DNA damage response (DDR). For example, it influences the strength of DNA repair proteins such as RAD51, ATM, or BRCA1, ensuring that the restoration machinery works at its best (Huang, 2021). Apart from this, it also mediates chromatin remodeling through the histone proteins (Shan et al., 2024).

4.5. The Significance in Oocyte Maturation

The deletion of HUWE1 in initial follicular stages causes oocyte death, leading to infertility. The absence of HUWE1 will cause failed oocyte maturation with meiotic defects. Thus, the protein is vital for the smooth functioning and maturation of oocytes (Kaur & Kurokawa, 2023).

4.6. HUWE1- The Mediator of Follicular and Embryonic Development

A key element of proper follicle formation, HUWE1 likely aids in preserving the equilibrium between granulosa cell growth and death by targeting pro-apoptotic genes (such as Mcl-1 or p53, depending on tissue context). HUWE1 supports zygotic genome activation (ZGA) and the development of the embryo by allowing the breakdown of maternal proteins that are no longer required. Embryos made from Huwe1-deficient oocytes failed to reach the blastocyst stage in the study conducted by (Kaur & Kurokawa, 2023). Meiotic halt, poor oocyte maturation, and infertility can all impact female reproductive activity (Biswas et al., 2021). Dysfunction could lead to infertility in both sexes. Therefore, by preserving a variety of reproductive processes in both males and females, HUWE1 acts as a checkpoint (Xiong et al., 2022).

5. Animal Model Studies (Knockout and Knockdown Studies)

Many knockout and knockdown experimental investigations demonstrated that HUWE1 is vital for spermatogenesis. An experimental knockout study conducted by (Eisa et al., 2020) was focused on HUWE1's function in the reproductive system of females. The findings indicated that HUWE1 is a special and important maternal factor that is essential for preserving the quality of embryos and oocytes. One of the studies conducted by (Fok et al., 2017) is based on animal models such as mice. Based on the study, mice's male germ cells' inactivation of the ubiquitin ligase Huwe1 in male germ cells caused spermatogonia to degenerate in neonates and adult mice to have a Sertoli cell-only phenotype. Reduced mitotic re-entry in Huwe1 mutant gonocytes prevented them from developing into spermatogonia. Cell degeneration occurred when Huwe1 was inactivated in the C18-4 cell line or primary spermatogonial culture. Higher amounts of histone H2AX and a higher DNA damage response were linked to the degeneration of Huwe1 deletion spermatogonia, which appeared to cause a mitotic collapse but did not cause apoptosis or senescence. Huwe1-depleted cells failed to degenerate after the spike in H2AX was inhibited. The collective findings specify that Huwe1 shows a previously unreported role in coordinating the male germline's physiological DNA damage response, assisting in the development and maintenance of spermatogonia.

The (Chen et al., 2016) carried out a similar study on animal models as mice, which states that HUWE1 is crucial for the development of preimplantation embryos in mice, and its dysregulation is linked to inadequate human embryo development. The study aimed to explore HUWE1's function in the early phases of embryonic development. The findings showed that preimplantation mouse embryos and gametes express Huwe1 in both the cytoplasm and nucleus. Huwe1 expression may be markedly elevated during the development of the mouse embryo by hypoxia (5% O2). Its knockdown decreased blastocyst formation, impeded normal embryonic development, and increased the no-of apoptotic cells in the HUWE1 knockdown group's embryos. The results of the human embryo staining indicated that the low-quality embryos had less HUWE1 staining. Additionally, the Western blot findings demonstrated that the villi of miscarried embryos had considerably lower levels of HUWE1 expression than the normal control, suggesting a link between poor embryo development and lower levels of HUWE1 expression. Human sperm HUWE1 expression was decreased by the oxidative reagent H_2O_2, suggesting that oxidative stress controls sperm HUWE1 expression. In short, these findings imply that the HUWE1 protein may aid in the development of preimplantation embryos and that dysregulated HUWE1 expression may be linked to defective embryo development and IVF clinic miscarriages.

6. Limitations and Future Perspectives

Although HUWE1's function in male fertility has been extensively studied, there are still a lot of unresolved concerns. The majority of our knowledge is derived from research on animals, particularly mice, and it's not always apparent how well these conclusions translate to people. The way that HUWE1 regulates the growth of sperm cells at every stage, from young stem cells to fully formed sperm, for instance, is not completely known.

The fact that HUWE1 appears to play distinct roles in various tissues presents another difficulty. It means that it is difficult to create drugs that safely target it. There are currently no particular drugs that can either block or raise HUWE1 function in the testis or ovary with an impact on other organs. To fully understand how HUWE1 functions and whether issues with this protein are contributing to male and female infertility, more research is required, especially with humans or human-like models.

7. Conclusions

The review highlighted the vital role of HUWE1 in gametogenesis. By preserving oocyte quality, controlling meiotic development, and promoting granulosa cell survival, HUWE1 is essential throughout oogenesis in the female reproductive system. Mice with oocyte-specific knockout experiments have shown that HUWE1 deficiency causes follicular degeneration, early embryonic arrest, and defective oocyte maturation. These results highlight the critical function of HUWE1 in initial embryonic growth as well as gametogenesis. In the male reproductive system, HUWE1 supports the maintenance of spermatogonial stem cells, regulates the stability of key proteins during spermatogenesis, facilitates chromatin remodeling, and contributes to DNA damage repair during meiosis. Loss or malfunction of HUWE1 causes meiotic arrest, increased germ cell death, lowered sperm production, and eventually male infertility, according to studies conducted in animal models. HUWE1 has potential as a biomarker for fertility evaluation and as a therapeutic target for managing infertility in humans due to its involvement in several important reproductive pathways. New reproductive healthcare diagnostic and treatment methods could be made possible by a deeper understanding of its biological mechanisms.

8. References

Bencivenga, D., Stampone, E., Vastante, A., Barahmeh, M., Della Ragione, F., & Borriello, A. (2022). An unanticipated modulation of cyclin-dependent kinase inhibitors: the role of long non-coding RNAs. Cells, 11(8), 1346.

Berruti, G. (2021). Destruction or reconstruction: a subtle liaison between the proteolytic and Signaling role of protein ubiquitination in spermatogenesis. In Molecular Mechanisms in Spermatogenesis (pp. 215–240). Springer.

Biswas, L., Tyc, K., El Yakoubi, W., Morgan, K., Xing, J., & Schindler, K. (2021). Meiosis interrupted: the genetics of female infertility via meiotic failure. Reproduction, 161(2), R13–R35.

Chen, L. J., Xu, W. M., Yang, M., Wang, K., Chen, Y., Huang, X. J., & Ma, Q. H. (2016). HUWE1 plays important role in mouse preimplantation embryo development and the dysregulation is associated with poor embryo development in humans. Scientific Reports, 6(June), 1–11. https://doi.org/10.1038/srep37928

Cruz Walma, D. A., Chen, Z., Bullock, A. N., & Yamada, K. M. (2022). Ubiquitin ligases: guardians of mammalian development. Nature Reviews Molecular Cell Biology, 23(5), 350–367.

Damgaard, R. B. (2021). The ubiquitin system: from cell signalling to disease biology and new therapeutic opportunities. Cell Death & Differentiation, 28(2), 423–426.

Eisa, A. A., Bang, S., Crawford, K. J., Murphy, E. M., Feng, W. W., Dey, S., Wells, W., Kon, N., Gu, W., & Mehlmann, L. M. (2020). X-linked Huwe1 is essential for oocyte maturation and preimplantation embryo development. Iscience, 23(9).

EMAN, R., TARIQ, M., NAZIR, N., AMIN, F., KHAN, H. A., IJAZ, M. U., AKBAR, A. L. I., & BIBI, M. (n.d.). Reproductive Biology: From Gametogenesis to Hormonal Regulation.

Fang, F., Iaquinta, P. J., Xia, N., Liu, L., Diao, L., & Reijo Pera, R. A. (2022). Transcriptional control of human gametogenesis. Human Reproduction Update, 28(3), 313–345.

Fok, K. L., Bose, R., Sheng, K., Chang, C. W., Katz-Egorov, M., Culty, M., Su, S., Yang, M., Ruan, Y. C., Chan, H. C., Iavarone, A., Lasorella, A., Cencic, R., Pelletier, J., Nagano, M., Xu, W., & Wing, S. S. (2017). Huwe1 regulates the establishment and maintenance of spermatogonia by suppressing DNA damage response. Endocrinology, 158(11), 4000–4016. https://doi.org/10.1210/en.2017-00396

Gavali, S., Liu, J., Li, X., & Paolino, M. (2021). Ubiquitination in T-cell activation and checkpoint inhibition: new avenues for targeted cancer immunotherapy. International Journal of Molecular Sciences, 22(19), 10800.

Houda, A., Nyaz, S., Sobhy, B. M., Bosilah, A. H., Romeo, M., Michael, J. P., & Eid, H. M. (2021). Seminiferous tubules and spermatogenesis. In Male reproductive anatomy. IntechOpen.

Huang, S. (2021). Characterization of the Functional Roles of the E3 Ligase HUWE1 in the Regulation of Poly [ADP-ribose] Polymerase 1 (PARP-1) under DNA Damage.

Huang, S., Cheng, A., Wang, M., Yin, Z., Huang, J., & Jia, R. (2022). Viruses utilize ubiquitination systems to escape TLR/RLR-mediated innate immunity. Frontiers in Immunology, 13, 1065211.

Kao, S.-H., Wu, H.-T., & Wu, K.-J. (2018). Ubiquitination by HUWE1 in tumorigenesis and beyond. Journal of Biomedical Science, 25(1), 67.

Kaur, S., & Kurokawa, M. (2023). Regulation of oocyte apoptosis: A view from gene knockout mice. International Journal of Molecular Sciences, 24(2), 1345.

Kelsall, I. R. (2022). Non-lysine ubiquitylation: Doing things differently. Frontiers in Molecular Biosciences, 9, 1008175.

Kirillova, A., Martazanova, B., Mishieva, N., & Semenova, M. (2021). Follicular waves in ontogenesis and female fertility. Biosystems, 210, 104558.

LaPlante, G., & Zhang, W. (2021). Targeting the ubiquitin-proteasome system for cancer therapeutics by small-molecule inhibitors. Cancers, 13(12), 3079.

Lee, J. M., Hammarén, H. M., Savitski, M. M., & Baek, S. H. (2023). Control of protein stability by post-translational modifications. Nature Communications, 14(1), 201.

Lin, Y., & Jin, X. (2023). Effect of ubiquitin protease system on DNA damage response in prostate cancer. Experimental and Therapeutic Medicine, 27(1), 33.

Liu, B., Wang, M., Cen, C., Shen, Z., Li, J., Cui, X., Zhao, X., Chen, M., & Gao, F. (2025). HUWE1 is involved in Sertoli cell polarity establishment by ubiquitination mediated degradation of WT1. Cellular and Molecular Life Sciences, 82(1), 271.
Lu, M., Zhang, Q.-C., Zhu, Z.-Y., Peng, F., Li, Z., Wang, Y., Li, X.-Y., Wang, Z.-W., Zhang, X.-J., & Zhou, L. (2023). An efficient approach to synthesize sterile allopolyploids through the combined reproduction mode of ameiotic oogenesis and sperm-egg fusion in the polyploid Carassius complex. Science Bulletin, 68(10), 1038–1050.
Luaces, J. P., Toro-Urrego, N., Otero-Losada, M., & Capani, F. (2023). What do we know about blood-testis barrier? current understanding of its structure and physiology. Frontiers in Cell and Developmental Biology, 11, 1114769.
Luo, S. Y. (2024). Characterizing protein modifications and interactions in viral infections.
Ma, L., Shen, W., Zhang, J., Ma, L., Shen, W., Shen, W., Ma, L., Zhang, J., & Zhang, J. (2023). The life cycle of the ovary. In Ovarian aging (pp. 7–33). Springer.
Müller, S. (2023). Investigations into the interplay between the ubiquitin-like modifier FAT10 and the E3 ligases HUWE1 or CHIP. Universität Konstanz.
O'Donnell, L., Smith, L. B., & Rebourcet, D. (2022). Sertoli cells as key drivers of testis function. Seminars in Cell & Developmental Biology, 121, 2–9.
Phelan, E. (2023). NDM-3: A Study of the Expression, Purification, and Characterisation of a B1-type metallo β-lactamase. National University of Ireland, Maynooth (Ireland).
Qi, L., Xu, X., & Qi, X. (2022). The giant E3 ligase HUWE1 is linked to tumorigenesis, spermatogenesis, intellectual disability, and inflammatory diseases. Frontiers in Cellular and Infection Microbiology, 12, 905906.
Qu, W., Liu, C., Xu, Y.-T., Xu, Y.-M., & Luo, M.-C. (2021). The formation and repair of DNA double-strand breaks in mammalian meiosis. Asian Journal of Andrology, 23(6), 572–579.
Santos-Rebouças, C. B., Boy, R., Fernandes, G. N. S., Gonçalves, A. P., Abdala, B. B., Gonzalez, L. G. C., Dos Santos, J. M., & Pimentel, M. M. G. (2023). A novel Xp11. 22 duplication involving HUWE1 in a male with syndromic intellectual disability and additional neurological findings. European Journal of Medical Genetics, 66(4), 104716.
Shan, X., Zhang, X., Huang, G., Lv, J., Ye, Z., Jiang, C., Jiang, X., Cheng, J., Lin, H., & Jiang, H. (2024). A novel SNP in HUWE1 promoter confers increased risk of NOA by affecting the RA/RARα pathway in Chinese individuals. Andrology, 12(2), 338–348.
Sun, A., Chen, Y., Tian, X., & Lin, Q. (2023). The role of HECT E3 ubiquitin ligases in colorectal cancer. Biomedicines, 11(2), 478.
Sun, A., Tian, X., Chen, Y., Yang, W., & Lin, Q. (2023). Emerging roles of the HECT E3 ubiquitin ligases in gastric cancer. Pathology and Oncology Research, 29, 1610931.
Tan, K., Song, H.-W., & Wilkinson, M. F. (n.d.). RHOX10 Drives Spermatogonial Stem Cell Establishment Through a Transcription Factor Signaling Cascade. Available at SSRN 3817801.
Wang, J., Zhou, Q., Ding, J., Yin, T., Ye, P., & Zhang, Y. (2022). The conceivable functions of protein ubiquitination and deubiquitination in reproduction. Frontiers in Physiology, 13, 886261.
Waqas, M. S. (2021). Spermatogenesis. Bovine Reproduction, 32–39.
Wasielak-Politowska, M., & Kordowitzki, P. (2022). Chromosome segregation in the oocyte: what goes wrong during aging. International Journal of Molecular Sciences, 23(5), 2880.
Wen, Y. (2021). Characterizatio of the Role of Tandem Ubiquitin Binding Motif (tUBM) of E3 Ligase HUWE1.
Xiong, Y., Yu, C., & Zhang, Q. (2022). Ubiquitin-proteasome system–regulated protein degradation in spermatogenesis. Cells, 11(6), 1058.
Xu, Y., Liu, X., Zeng, W., Zhu, Y., Dong, J., Wu, F., Chen, C., Sharma, S., & Lin, Y. (2024). DOCK1 insufficiency disrupts trophoblast function and pregnancy outcomes via DUSP4-ERK pathway. Life Science Alliance, 7(2).
Yang, Q., Zhao, J., Chen, D., & Wang, Y. (2021). E3 ubiquitin ligases: styles, structures and functions. Molecular Biomedicine, 2(1), 23.
Yuan, Y., Wang, L., Zhao, X., Wang, J., Zhang, M., Ma, Q., Wei, S., Yan, Z., Cheng, Y., & Chen, X. (2022). The E3 ubiquitin ligase HUWE1 acts through the N-Myc-DLL1-NOTCH1 signaling axis to suppress glioblastoma progression. Cancer Communications, 42(9), 868–886.
Zhai, F., Ma, X., Yan, L., & Qiao, J. (2023). The molecular genetics of oogenesis. In Human reproductive and prenatal genetics (pp. 145–163). Elsevier.

Zhou, M., Fang, R., Colson, L., Donovan, K. A., Hunkeler, M., Song, Y., Zhang, C., Chen, S., Lee, D., & Bradshaw, G. A. (2023). HUWE1 amplifies ubiquitin modifications to broadly stimulate clearance of proteins and aggregates. BioRxiv, 2005–2023.