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Testicular Seminoma and Hippo Signaling Pathway

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Abstract

The Hippo signaling pathway is a highly conserved regulator of tissue development and regeneration that controls organ size, primarily through the control of cell proliferation and apoptosis. Dysregulation of this pathway contributes to tumorigenesis in multiple human cancers; however, its role in testicular cancer—particularly seminoma—remains insufficiently characterized. Testicular germ cell tumors (TGCTs) are the most common malignancies in young adult men, with seminoma representing the predominant histological subtype. In this review, we summarize the molecular architecture of the Hippo signaling pathway and critically evaluate current evidence linking Hippo pathway components to testicular biology and seminoma pathogenesis, in accordance with the 2022 World Health Organization (WHO) classification of testicular tumors. Particular emphasis is placed on mixed germ cell tumors, the relative proportion of seminoma among TGCTs, and emerging therapeutic strategies targeting Yes-associated protein / Transcriptional coactivator with PDZ-binding motif (YAP/TAZ) signaling. We further integrate recent translational findings demonstrating the anti-cancer effects of verteporfin in human seminoma TCam-2 cells, highlighting the Hippo pathway as a promising and context-dependent therapeutic target in testicular seminoma.

Keywords: Testicular seminoma, Testicular germ cell tumors, Hippo signaling, pathway, YAP/TAZ, verteporfin.

TESTIS

The testis is the male gonad responsible for spermatogenesis and steroidogenesis (1,2). It consists of seminiferous tubules, where germ cell development occurs, and interstitial tissue containing Leydig cells that produce testosterone (3,4). Sertoli cells within the seminiferous tubules support germ cell differentiation and, through their tight interconnections, form the blood-testis barrier, which is essential for immune privilege and spermatogenic integrity (5-8). Leydig cells are the source of androgens or testosterone in males (9).

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Spermatogenesis and Spermiogenesis

Spermatogenesis is a highly regulated, multi-stage process involving mitotic proliferation, meiotic division, and post-meiotic differentiation (spermiogenesis), ultimately producing mature spermatozoa (4,10). Sertoli-germ cell interactions and tightly regulated signaling networks ensure proper progression of this process (11,12). The time required for the spermatogonia to develop into mature sperm is approximately 64 days (13). Spermiogenesis is the final phase of spermatogenesis which differentiation of haploid germ cells to motile, fertilization-competent spermatozoa occur.

TESTICULAR CANCER

Testicular cancer is the most common type of malignancy in men aged between 15 and 35 years (14,15) accounting for approximately 1% of all male cancers (16,17). The majority (>95%) are testicular germ cell tumors (TGCTs), whose pathogenesis involves a complex interplay between genetic susceptibility, disrupted germ cell differentiation, and environmental influences (16,17).

Testicular Cancer Development

Despite extensive research, the etiology of testicular germ cell tumors (TGCTs) remains incompletely understood. Both environmental and genetic factors have been implicated in TGCT development, with increased risk observed in individuals with cryptorchidism, familial TGCT history, Klinefelter syndrome, testicular dysgenesis, testicular atrophy, inguinal hernia, and hydrocele (18-21). Genome-wide association studies have further identified multiple single nucleotide polymorphisms associated with TGCT susceptibility, supporting a strong genetic contribution to disease risk (22,23). Although environmental influences such as androgen disruption and perinatal or lifestyle factors have been proposed, their direct relationship with TGCT remains unclear, suggesting that tumorigenesis likely arises from the combined effects of microenvironmental and epigenetic alterations (24-26).

Developmentally, TGCTs are thought to originate from germ cell neoplasia *in situ* (GCNIS), arising when primordial germ cells or gonocytes fail to differentiate into pre-spermatogonia during fetal or early postnatal development. This differentiation arrest may result from genetic abnormalities or exposure to endocrine-disrupting environmental factors, including anti-androgens and xenoestrogens (27-29). While it remains debated whether GCNIS originates from arrested spermatogonial cells or from reprogrammed adult germ cells, the high differentiation potential of adult spermatogonia lends support to the latter hypothesis (30).

Testicular Cancer Types

According to the 2022 World Health Organization (WHO) classification of tumors of the urinary system and male genital organs, testicular tumors are broadly categorized into germ cell tumors (GCTs), sex cord-stromal tumors, and a heterogeneous group of other rare tumors (31). Germ cell tumors account for more than 95% of all testicular malignancies and represent the most clinically significant category (16,32,33).

Testicular GCTs are further divided into two major biological groups based on their association with GCNIS:

- GCNIS-related tumors, which represent the vast majority of postpubertal TGCTs and include seminomas *and* non-seminomatous germ cell tumors *(*NSGCTs*)*, and
- Non-GCNIS-related tumors. which typically occur in prepubertal children or older adults and follow distinct pathogenetic mechanisms (34,35).

Seminoma is the most common histological subtype of TGCT, accounting for approximately 50–55% of cases (36). Seminomas are composed of relatively uniform cells resembling primordial germ cells or gonocytes and typically present in young to middle-aged adults. Histologically, seminomas are characterized by large polygonal cells with clear cytoplasm, centrally located nuclei, and prominent nucleoli, arranged in sheets or lobules separated by fibrous septa containing lymphocytic infiltrates (37). Serum tumor markers are usually normal, although mild elevation of β-human chorionic gonadotropin (β-hCG) may be observed due to the presence of syncytiotrophoblastic giant cells (36,37).

Non-seminomatous germ cell tumors comprise a heterogeneous group that includes embryonal carcinoma, yolk sac tumor, choriocarcinoma, and teratoma. These tumors may occur as pure forms but more commonly present as components of mixed germ cell tumors (38). Embryonal carcinoma is an aggressive malignant tumor composed of poorly differentiated epithelial cells with high mitotic activity (39). Yolk sac tumor is the most frequent TGCT in infancy and early childhood and is characterized by Schiller-Duval bodies and elevated alpha-fetoprotein (AFP) levels (40,41). Choriocarcinoma is a rare but highly aggressive tumor with early hematogenous dissemination and markedly elevated β-hCG levels (42-44). Teratomas consist of differentiated tissues derived from two or three embryonic germ layers and may be benign or malignant depending on patient age and associated tumor components (45).

Importantly, mixed germ cell tumors represent approximately 30–40% of all TGCTs and contain variable proportions of seminomatous and non-seminomatous elements

(33,38). The identification of mixed histology is clinically critical, as even a minor non-seminomatous component dictates treatment strategies and prognosis. Therefore, comprehensive histopathological sampling and accurate classification according to WHO criteria are essential for optimal patient management (42-44,46).

Sex cord-stromal tumors, including Leydig cell and Sertoli cell tumors, account for less than 5% of testicular neoplasms. These tumors are usually benign and hormonally active in some cases, leading to endocrine manifestations such as gynecomastia or precocious puberty (47). Malignant transformation is rare but has been reported, particularly in Leydig cell tumors (31,47).

Overall, the 2022 WHO classification emphasizes the biological heterogeneity of testicular tumors and highlights the importance of GCNIS status, mixed tumor composition, and precise histopathological diagnosis. This updated framework provides a critical foundation for understanding tumor behavior, guiding clinical decision-making, and interpreting molecular pathways—such as Hippo signaling—that may differentially contribute to seminoma and non-seminomatous TGCT pathogenesis (32,34).

HIPPO SIGNALING PATHWAY

The Hippo signaling pathway was originally identified in *Drosophila melanogaster* as a tumor-suppressive pathway and is highly conserved in mammals, including humans and mice (48). It functions as a central regulator of organ size and tissue homeostasis by integrating diverse upstream signals such as cell polarity, cell-cell contact, metabolic status, mechanical cues, and G-protein-coupled receptor signaling (48). Through these inputs, Hippo signaling limits cell proliferation, migration, and differentiation during development, while its dysregulation promotes abnormal tissue growth and tumorigenesis (48).

In mammals, Hippo signaling is mediated by a core kinase cascade in which mammalian STE20-like protein kinases 1/2 (MST1 and MST2 kinases), activated by autophosphorylation and upstream TAO kinases (TAOK1/2/3), phosphorylate and activate large tumor suppressor kinases 1/2 (LATS1/2) (48-52). The tumor suppressor neurofibromin 2 (NF2) (also known as Merlin) facilitates this process by recruiting LATS1/2 to the plasma membrane, enabling efficient mammalian STE20-like

Table 1. Hippo signaling pathway proteins and roles in cancer.

Protein	Class/Function	Role in active hippo pathway	Role in cancer	Reference
MST1/2 (STK4/3)	Serine/Threonine kinases	Phosphorylate and activate LATS1/2 and MOB1	Tumor suppressor (Inactivation promotes tumorigenesis)	(48)
SAV1	Adaptor protein/ Scaffold	Binds MST1/2 and LATS1/2 to facilitate LATS phosphorylation	Tumor suppressor	(49,50)
LATS1/2	Serine/Threonine kinases	Phosphorylate and inactivate YAP and TAZ	Tumor suppressor	(51)
MOB1A/B	Adaptor protein/ Cofactor	Associates with LATS1/2 to potentiate their kinase activity	Tumor suppressor	(52)
YAP	Transcriptional coactivator	Phosphorylated by LATS1/2, leading to cytoplasmic retention and degradation	Oncogene (Nuclear localization promotes cell proliferation/ survival)	(53-55)
TAZ (WWTR1)	Transcriptional coactivator	Phosphorylated by LATS1/2, leading to cytoplasmic retention and degradation	Oncogene (Nuclear localization promotes cell proliferation/ survival)	(56)
TEAD1-4	Transcription factors	Partner with YAP/TAZ in the nucleus to drive gene expression	Key oncogenic mediators of YAP/ TAZ activity	(57)

MST1/2: Mammalian STE20-like protein kinase 1/2, **STK4/3:** Serine/threonine kinase 4/3, **SAV1:** Salvador homolog 1, **LATS1/2:** Large tumor suppressor kinase 1/2, **MOB1A/B:** Mps one binder kinase activator-like 1A/1B, **YAP:** Yes-associated protein, **TAZ:** Transcriptional coactivator with PDZ-binding motif (WWTR1), **TEAD:** TEA domain transcription factor.

protein kinase 1/2 (MST1/2)-mediated phosphorylation (26). Activated LATS1/2 subsequently phosphorylate the transcriptional coactivators yes-associated protein (YAP) and (transcriptional coactivator with PDZ-binding motif) (TAZ), leading to their cytoplasmic retention or degradation and suppression of TEA domain transcription factor (TEAD)-dependent gene transcription (53,55-57). When Hippo signaling is inactive, unphosphorylated YAP and TAZ translocate to the nucleus, where they interact with TEAD transcription factors to induce genes involved in cell proliferation, migration, and survival (52-56) (Table 1).

The Hippo signaling pathway is organized by cell or tissue properties such as apicobasal polarity, mechanotransduction, cell-cell contact, and contact inhibition. Also, the Hippo signaling pathway and its components regulate very important processes such as cell viability, cell proliferation, cell competition, preservation of stem cell characteristics, regeneration, and metastasis (48). This pathway is conserved in mammals and has an important role in limiting tumor growth in cancer development. Regulation of the Hippo signaling pathway, therefore, presents a potential therapeutic case for treating cancer, but the targeted pathway needs to be explored in more detail (57-59).

Hippo Signaling Pathway in Male Reproductive System

Limited studies have examined Hippo signaling in the male reproductive system. In mice, genetic deletion of key Hippo components such as YAP, LATS1/2, or TAZ results in embryonic lethality, impaired postnatal development, or reduced fertility, highlighting their essential roles in testicular development and endocrine regulation (60-62). YAP and TAZ regulate genes involved in sex differentiation and early spermatogenesis, and Hippo pathway proteins have been identified in Sertoli cells across multiple species, where YAP controls cyclic AMP signaling, proliferation, and apoptosis (60,63). Although indirect evidence suggests a role for Hippo signaling in germ cell regulation, including miRNA-mediated inhibition of LATS2 and high YAP expression in spermatogonia (61). Its function in human testicular tissue remains unexplored, with no studies to date evaluating Hippo pathway protein expression in the normal human testis, aside from prostate cancer-related reports (64).

Hippo Signaling Pathway in Human Cancer

The Hippo signaling pathway functions as a central regulator of cellular homeostasis by integrating biochemical and mechanical cues to control proliferation, apoptosis, stemness, and tissue architecture. Canonically, activa-

Table 2. Hippo pathways inhibitors and key findings/status in cancer treatment.

Inhibitor/ Drug Class	Target(s)	Lead cancer indication(s) in trials	Key findings/Status	Clinical trial ID (NCT)	Reference
VT3989	YAP/TAZ-TEAD Interaction (Non-covalent TEAD Ligand)	Malignant mesothelioma (MPM), Non-small cell lung cancer (NSCLC), other advanced solid tumors	First-in-human Phase 1 trials showed early efficacy signals and durable responses in NF2-mutated and wild-type mesothelioma.	NCT04665206 (Clinical trial ID)	(77)
IAG933	YAP/TAZ-TEAD Interaction (Orally Bioavailable Inhibitor)	Various solid tumors with Hippo/YAP pathway activation.	Preclinical data shows potent, specific inhibition of the YAP/TAZ-TEAD axis and strong antitumor effects, positioning it for upcoming clinical studies.	NCT05590918 (Example trial ID for a related next-gen TEAD inhibitor)	(78)
VP	YAP/TAZ-TEAD Interaction (Disrupts complex, YAP degradation)	Glioblastoma, Pancreatic cancer, Ocular/Uveal melanoma (Mostly used in photodynamic therapy or PDT)	Preclinical studies show light-independent inhibition of YAP/TAZ function in many tumor types. Clinical trials mainly use it as a photosensitizer in PDT, but some Glioblastoma trials test its single-agent YAP-inhibitory activity.	NCT04590664 (Verteporfin for recurrent glioblastoma-light-independent)	(79)
MRK-A	YAP/TAZ-TEAD Interaction (Preclinical Compound)	Preclinical/Development (Focus on mesothelioma, glioblastoma, sarcoma)	Inhibits the YAP/TAZ-TEAD complex and suppresses tumor growth in NF2-deficient mesothelioma xenografts *in vivo*.		(80-82)

YAP: Yes-associated protein, **TAZ:** Transcriptional coactivator with PDZ-binding motif, **TEAD:** TEA domain transcription factor, **NF2:** Neurofibromin 2, **NSCLC:** Non-small cell lung cancer, **MPM:** Malignant pleural mesothelioma, **VP:** Verteporfin, **PDT:** Photodynamic therapy.

tion of the MST1/2-LATS1/2 kinase cascade restricts nuclear YAP/TAZ activity, thereby limiting TEAD-dependent transcription of genes that promote cell cycle progression and survival. Disruption of this regulatory axis through genetic mutations or functional suppression of upstream Hippo components leads to constitutive YAP/TAZ activation and uncontrolled cell proliferation, a phenomenon consistently observed in both *Drosophila* and mammalian tumor models (58,65-67).

Beyond proliferation, YAP and TAZ exert profound effects on tumor cell plasticity by promoting stem cell-like transcriptional programs. Elevated YAP/TAZ activity has been documented in embryonic, mesenchymal, and cancer stem cells, where it sustains self-renewal capacity and inhibits differentiation. Mechanistically, YAP/TAZ regulate pluripotency-associated gene networks and cooperate with TEAD transcription factors to maintain progenitor states, thereby increasing tumorigenic potential and resistance to therapy (65-68). These stemness-promoting effects are further reinforced by YAP/TAZ-mediated loss of contact inhibition and disruption of epithelial tissue architecture, both hallmark features of malignant transformation (69,70).

Hippo signaling is also a key mechanotransduction pathway that senses changes in extracellular matrix stiffness, cell-cell adhesion, and cytoskeletal tension. Mechanical inactivation of the Hippo kinase cascade results in nuclear accumulation of YAP/TAZ, which in turn drives transcriptional programs favoring invasion, migration, and metastatic progression. Increased YAP/TAZ activity has been correlated with aggressive and metastatic phenotypes in breast and prostate cancers, supporting a role for Hippo pathway dysregulation in tumor dissemination (70).

In regenerative contexts, transient suppression of Hippo signaling enables tissue repair by activating YAP/TAZ-dependent progenitor expansion. However, chronic or unrestrained activation of this regenerative program can promote oncogenesis, particularly in tissues with high regenerative capacity. Experimental models demonstrate that sustained YAP/TAZ activation during repeated injury or regeneration drives tumor formation, linking Hippo pathway dysregulation to regeneration-associated carcinogenesis (71-76).

Despite extensive evidence implicating Hippo signaling in diverse human cancers, its role in testicular tumors has

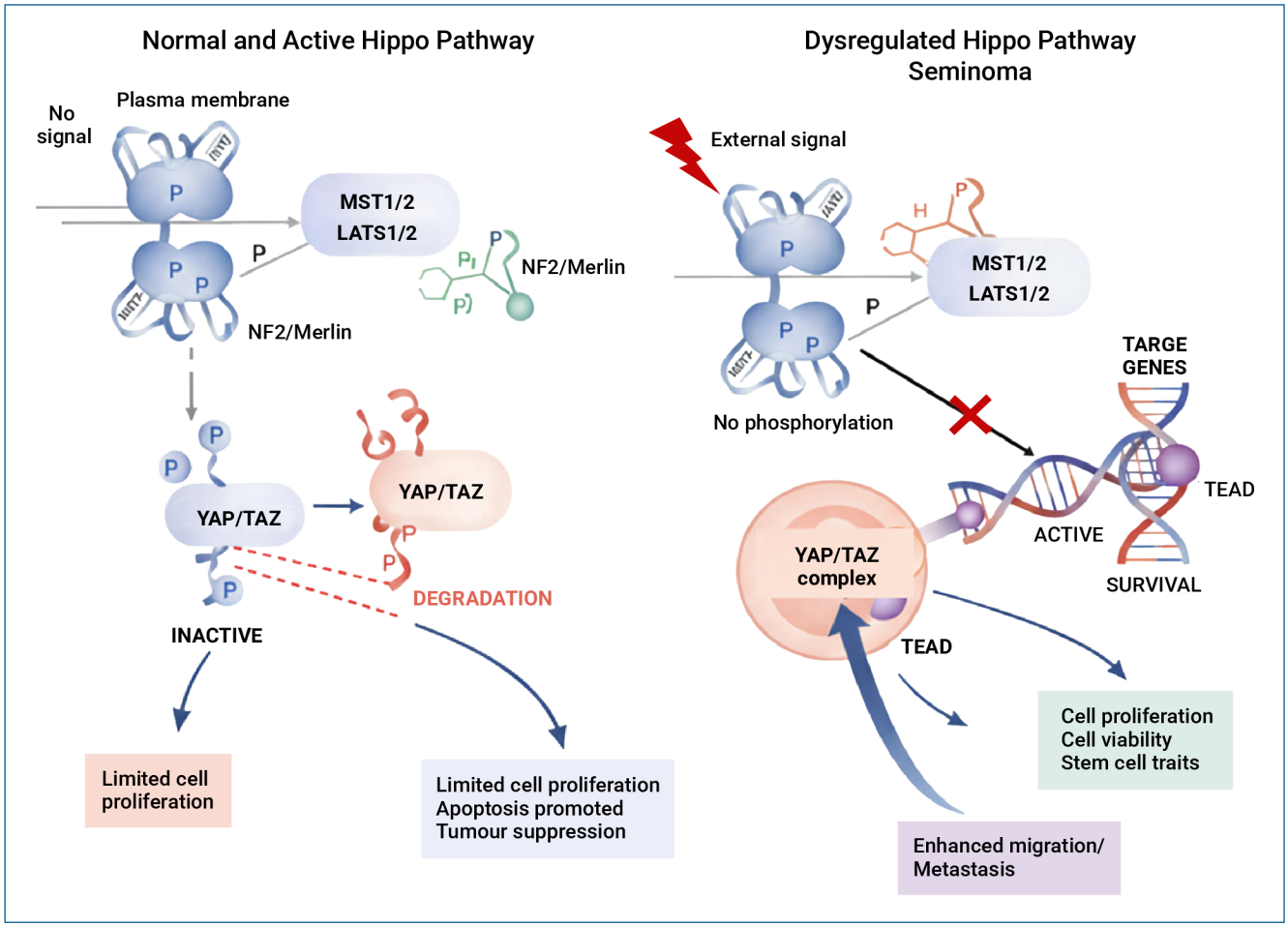

FIGURE 1. Normal and active Hippo signaling pathway with dysregulated Hippo pathway.

remained largely unexplored. In this context, our findings demonstrate that Hippo pathway components exhibit tissue-specific localization patterns in the human testis and that pharmacological inhibition of YAP-TEAD interaction by verteporfin suppresses proliferation and migration while inducing apoptosis in seminoma-derived TCam-2 cells. Notably, these effects occur primarily through post-transcriptional modulation and cytoplasmic sequestration of YAP/TAZ, highlighting a mechanistic vulnerability of seminoma cells to Hippo pathway targeting. Collectively, these data identify Hippo signaling as a context-dependent regulator of seminoma biology and support verteporfin as a promising therapeutic strategy for precision targeting of testicular cancer (77-82) (Table 2).

CONCLUSION

This review highlights the Hippo signaling pathway as a critical yet understudied regulator of testicular seminoma biology. Aberrant activation of YAP/TAZ has been implicated in tumor cell survival, proliferation, and therapy resistance across multiple cancer types, and emerging evidence suggests that similar mechanisms operate in seminoma. Importantly, experimental data using the seminoma-derived TCam-2 cell line demonstrate that pharmacological targeting of Hippo signaling with verteporfin exerts significant anti-cancer effects by suppressing YAP/TAZ activity and inducing apoptosis (77-82).

Collectively, these findings support the Hippo signaling pathway as a promising molecular target in testicular seminoma and provide a strong rationale for future translational and clinical studies aimed at precision therapy in TGCTs (Figure 1). Integration of WHO 2022 tumor classification with molecular pathway analysis will be essential for identifying patients most likely to benefit from Hippo pathway-directed therapeutic strategies.

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