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Mechanisms and etiology of male health disorders: hormones, cancer, and fertility

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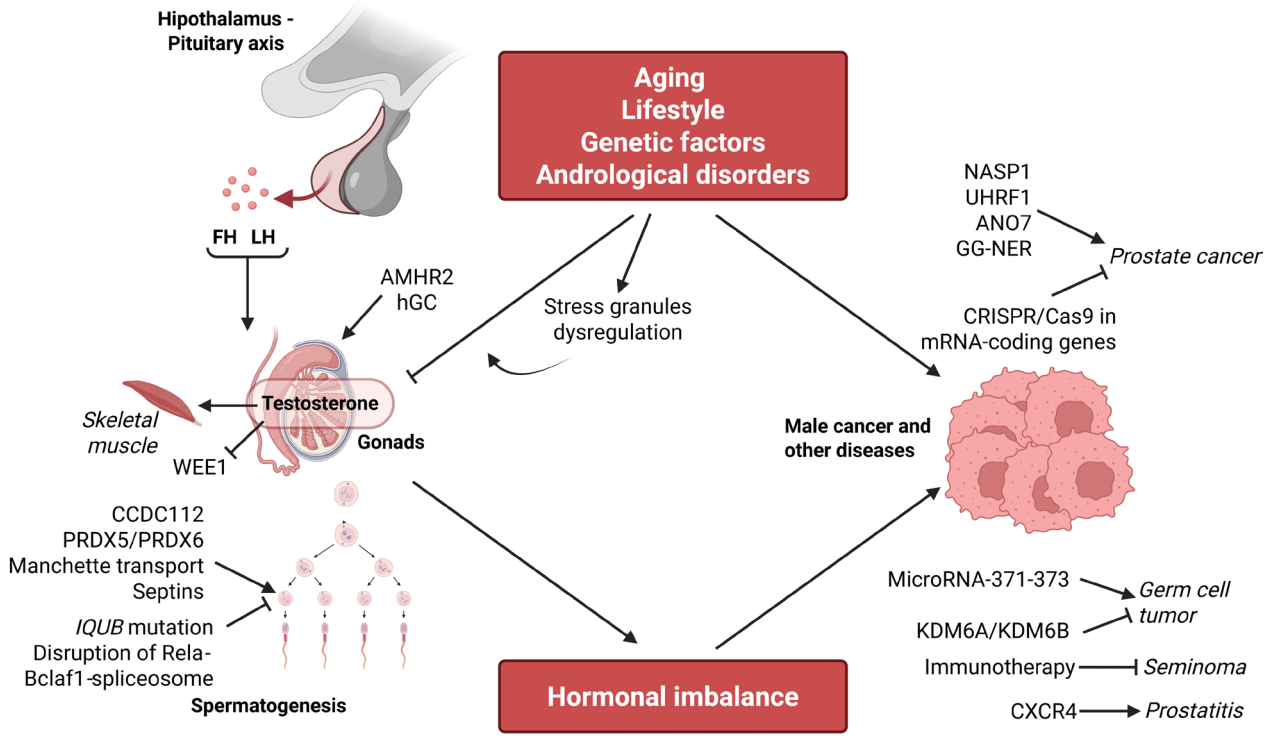
Graphical abstract



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Normal male physiology is orchestrated by a complex interplay of endocrine signals, paracrine growth factors, and tightly regulated inter- and intra-cellular communications that ensure proper testicular function and spermatogenesis [1]. Aging and environmental factors, such as obesity-induced hypogonadism and exposure to endocrine-disrupting agents, further modulate reproductive health by altering hormonal feedback loops and the epigenetic landscape [2, 3]. Dysregulation of these homeostatic mechanisms underlies the pathogenesis of male health disorders ranging from late-onset hypogonadism and idiopathic infertility to hormone-driven cancers of the prostate and testis [4]. Recent studies have illuminated how gonadal steroids shape the hypothalamic–pituitary–adrenal axis, unveiling sex-specific regulatory circuits that link stress responses to reproductive function [5, 6]. The etiology of prostate cancer involves a confluence of genetic predispositions, somatic mutations in DNA repair genes, and dysregulated cell-signaling pathways that drive aberrant proliferation and survival [7, 8]. Likewise, the pathobiology of testicular germ cell tumors implicates developmental aberrations in germ cell maturation and characteristic cytogenetic alterations, such as isochromosome 12p, in tumor initiation and progression [9, 10]. Finally, emerging evidence on epigenetic inheritance demonstrates that paternal lifestyle and environmental exposures can induce heritable modifications in sperm, with transgenerational impacts on offspring health and fertility [11, 12]. Collectively, these insights provide a molecular framework for understanding male health disorders and highlight novel avenues for targeted therapeutic interventions.

Building on the endocrine framework outlined above, Gentile et al. dissect the androgen/androgen receptor axis in sarcopenia, demonstrating that age-related androgen decline not only accelerates muscle catabolism via inflammatory mediators but also unveils specific signaling nodes—such as disrupted AR-mediated anabolic pathways, that could be harnessed for targeted myoprotective therapies [13]. Li and colleagues shine light on stress granules as dynamic guardians of germ cell integrity: by mapping the eIF2α-dependent assembly and disassembly of SGs under heat, hypoxia, and chemical insults, they identify SG modulation as a prospective intervention to preserve spermatogenesis in increasingly polluted and thermally stressed environments [14].

In prostate cancer research, Löf et al. uncover ANO7 as a linchpin of metabolic reprogramming, shifting tumor cells from oxidative phosphorylation to glycolysis and remodeling lipid profiles—a dual signature that not only differentiates aggressive disease but also suggests metabolic vulnerabilities for precision treatment [15]. In another study, Zhang et al. reveal CXCR4's role in steering macrophage M1 polarization through PI3K/AKT/mTOR–c-MYC–PFKFB3 signaling, linking chronic inflammation to prostate fibrosis; this mechanistic insight paves the way for CXCR4 antagonists to attenuate fibrotic progression in prostatitis patients [16].

Focusing on the role of epigenetic regulation in prostate cancer, Li et al. describes that UHRF1 promotes prostate cancer progression by forming phase-sparated nuclear condensates that recruit DNMT1 to silence tumor supressor genes via DNA methylation [17]. Moreover, the study performed by Feng and colleagues reveals that Nuclear autoantigenic sperm protein (NASP) is critical for maintaining AR function and chromatin architecture in castration-resistant prostate cancer cells. NASP knockdown disrupts AR-target gene expression, increases chromatin accessibility, alters high-order chromatin structure, and impairs AR rebinding [18].

Addressing therapy resistance, Zhong and co-workers demonstrate that heightened GG-NER activity portends poor enzalutamide response and that ACTL6A inhibition restores drug sensitivity—offering both a prognostic biomarker (NECGS) and a new therapeutic target in refractory prostate tumors [19]. In this frame, Shokry et al. take an epigenetic tack in testicular germ cell tumors, showing that inhibition of polycomb demethylases KDM6A/B via GSK-J4 synergizes with cisplatin, amplifying p53-driven apoptosis—a strategy that could reduce cisplatin dosage and long-term toxicity in young patients [20]. Tavares and colleagues also focused their work on testicular germ cell tumors, particularly in the secretion of the miR-371–373 cluster into extracellular vesicles. These results support the role of extracellular vesicles as a major source of circulating biomarkers, except in teratoma cases [21].

In seminoma, Cui et al. develop an immune-gene signature (CTLA4, SNX17, TMX1) that robustly predicts progression-free survival and guides immunotherapy selection, while nominating compounds like Rutin and ICG-001 for targeted intervention, demonstrating the power of integrative immunogenomics to transform salvage therapy in cisplatin-resistant cases [22]. Tabibian et al. review CRISPR/Cas9 breakthroughs in prostate cancer, spotlighting how precise editing of AR pathway and PI3K/AKT/mTOR components can thwart castration resistance, underscoring CRISPR's imminent clinical translation [23].

Expanding beyond mammals, Zhao et al. decode sex determination in spotted knifejaw, revealing amhr2 dosage as the molecular "rheostat" of male differentiation—an evolutionary paradigm that enriches our understanding of vertebrate sex-chromosome diversity and may inform aquaculture breeding strategies [24]. Furthermore, Zhai and colleagues show that androgen blockade disturbs Sertoli cell homeostasis via Wee1 and Lfng dysregulation, pinpointing new molecular targets to mitigate the adverse reproductive effects of anti-androgen

therapies [25]. Moreover, the review published by Gao and collaborators highlights the critical role of the manchette, a transient microtubule- and actin-based structure, in sperm head shaping and flagellar assembly during spermatogenesis. It summarizes current knowledge on manchette dynamics, intra-manchette transport, related genetic factors, and their implications in male infertility [26].

On gonadotoxic insults, Zhou et al. define an IR-induced Rela–Bclaf1–spliceosome axis whose disruption undermines primary spermatocyte differentiation—and demonstrate NF-κB agonists as radioprotective agents, a finding with immediate relevance for preserving fertility in male cancer patients undergoing radiotherapy [27]. Mostek-Majewska et al. characterize cryopreservation-induced PRDX5/6 oligomerization in bull sperm, offering mechanistic targets, such as TLR4-mediated peroxiredoxin trafficking, to enhance post-thaw viability in both animal breeding and human assisted reproduction [28]. Furthermore, Graffeo and colleagues identifies CCDC112 as essential for male fertility in mice, playing a critical role in mitochondrial sheath formation, midpiece maturation, and proper sperm motility. Loss of CCDC112 impairs mitochondrial structure and function, disrupts sperm movement and fertilization capacity, and reveals a previously unrecognized process of epididymal midpiece maturation during sperm transit [29].

Hu et al. identify an IQUB frameshift mutation that abolishes radial spoke 1 assembly, causally linking this defect to asthenozoospermia while validating ICSI as an effective remedy, expanding the genetic etiology of male infertility and refining patient counseling and treatment [30]. Al-Ali and co-authors comprehensively review septins in cytoskeletal dynamics, fertilization, and early embryogenesis, spotlighting septin complexes as untapped modulators, thus charting new directions for improving embryo viability in IVF protocols [31]. Finally, Errico et al. establish an in vitro hCG response model of cryptorchid gubernacular cells, revealing age-dependent proliferative and angiogenic differences that argue for personalized timing of adjuvant hormone therapy post-orchiopexy [32].

Conclusion and future directions

Together, these studies push the frontier of male health research by uncovering molecular culprits, from hormonal axes and stress granules to epigenetic modifiers and immune signatures, and translating them into actionable biomarkers and therapeutic targets. The diversity of models and approaches underscores a unifying theme: restoring homeostasis requires precision interventions tailored to the underlying molecular pathology. Moving forward, integrating multi-omics with high-throughput functional screens, organoid and in vivo disease models, and CRISPR-based perturbations will be pivotal to validate these targets and accelerate the translation of bench-side discoveries into clinically effective, personalized treatments for male health disorders.

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Declarations

Competing interests
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