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The testicular IL-18 system in experimental systemic inflammation: Evidence and unresolved questions

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ABSTRACT

Interleukin (IL)-18 is constitutively expressed in multiple testicular compartments and is regulated during systemic inflammation. This review examines how the testicular IL-18 system may contribute to inflammation-associated changes in germ cells and testicular somatic cells. Basal studies indicate that IL-18, its receptor components, and IL-18-binding protein (IL-18BP) are present in the testis, while experimental inflammatory stimulation alters components of the testicular IL-18 system. Evidence from primary cells and endotoxemia models indicates local IL-18 inducibility and increased circulating IL-18, but the relative contributions of local and circulating sources to bioavailable testicular IL-18 remain undefined. Functional studies further indicate that IL-18-associated responses vary with inflammatory and cellular context. In separate mouse endotoxemia experiments using different lipopolysaccharide (LPS) doses, global IL-18 deficiency was associated with less germ-cell apoptosis at 12 h but greater apoptosis at 48 h. In cell-based studies, recombinant IL-18 induced apoptosis-related responses in TM3 Leydig cells, whereas TM4 Sertoli cells remained viable despite transcriptional responsiveness. Separate IL-6 and LPS studies demonstrate barrier-related dysfunction in Sertoli-cell models, but direct IL-18 effects on blood–testis barrier function were not tested in the reviewed studies. Collectively, the evidence is consistent with a working model in which IL-18-associated testicular responses vary across inflammatory and cellular contexts, rather than showing a uniformly pro-apoptotic pattern. Temporally controlled and cell-specific studies, together with longitudinal assessment of IL-18/IL-18BP and reproductive function in severe systemic inflammation, should clarify the biological and translational relevance of the testicular IL-18 system.

1. Introduction

Systemic inflammatory states can affect male reproductive function, including spermatogenesis, steroidogenesis, and testicular immune regulation (Wang et al., 2019; Fomichova et al., 2025). Testicular histopathological abnormalities have been reported in fatal COVID-19 (Duarte-Neto et al., 2022), while semen impairment has been described after recovery (Gacci et al., 2021); these findings are consistent with a systematic review (Cannarella et al., 2024). In experimental models, systemic lipopolysaccharide (LPS) exposure induces germ-cell apoptosis and transient disturbances in sperm concentration and motility (Kajihara et al., 2006). Another model demonstrated transient testosterone suppression and, in some settings, longer-lasting disruption of the blood-testis barrier (BTB) and spermatogenesis (Wang et al., 2019). Across LPS and other testicular-inflammation models, implicated mechanisms include death-receptor and mitochondrial signaling, reactive oxygen and nitrogen species, and altered junctional organization (Theas et al., 2006; Cheng and Mruk, 2012; Theas, 2018).

Interleukin (IL)-18 is an IL-1-family cytokine with homeostatic and inflammatory functions (Okamura et al., 1995; Landy et al., 2024; Novick, 2024). IL-18 is of interest in the testis because components of the IL-18 system are constitutively present in germ cells, Leydig cells, Sertoli cells, and interstitial or peritubular compartments (Strand et al., 2005; Rozwadowska et al., 2007; Abu Elhija et al., 2008b, 2008d; Komsky et al., 2012). Inflammatory stimulation can increase testicular IL-18 and alter caspase-1/ICE and IL-18Rα expression, indicating that

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this constitutive system is responsive to systemic inflammatory stress (Abu Elhija et al., 2008c). Studies have linked IL-18 status or recombinant IL-18 exposure to different responses in germ-cell, Leydig-cell, and Sertoli-cell settings (Inoue et al., 2015, 2020, 2023). Together with the stage-restricted response to recombinant IL-18 reported in rat seminiferous tubules (Strand et al., 2005), these observations suggest that IL-18 is not simply an inducible inflammatory mediator but may participate in testicular cellular responses in a context-dependent manner.

Previous work has reviewed IL-18 in reproductive endocrine and immune disorders (Shan et al., 2025), but focused synthesis of its role in testicular responses to systemic inflammation remains limited. This narrative review examines experimental evidence on the testicular IL-18 system during acute systemic inflammation, with emphasis on endotoxemia and IL-18-associated responses in germ-cell and somatic-cell compartments (Abu Elhija et al., 2008a, 2008c; Inoue et al., 2015, 2020, 2023). Basal and human studies inform interpretation and translation of these experimental findings (Strand et al., 2005; Rozwadowska et al., 2007; Komsky et al., 2012). Chronic metabolic inflammation, primary testicular infection, and toxicant injury are excluded unless they clarify IL-18 biology or inflammation-associated testicular responses. We focus on how IL-18 source and availability, inflammatory timing, and cellular context may explain testicular responses.

To identify relevant studies, we searched PubMed, Scopus, and Web of Science through October 20, 2026, using “interleukin-18” or “IL-18” together with “testis,” “germ cell,” “Leydig cell,” or “Sertoli cell.” Additional searches combined these terms with “inflammation,” “lipopolysaccharide,” “LPS,” “endotoxemia,” or “sepsis.” Separate searches addressed human seminal studies (IL-18 and “semen”) and IL-18BP (“IL-18BP” or “IL-18 binding protein” combined with “testis,” “testicular,” “Leydig,” “Sertoli,” or “spermatogenesis”). Eligible primary studies examined (i) the testicular IL-18 system during experimental systemic inflammation, (ii) IL-18, IL-18BP, or IL-18 receptors in mammalian testicular tissues or cells, or (iii) these components in human testicular or seminal samples. Primary studies outside these categories or using non-mammalian models were excluded; contextual literature was considered separately. The study selection process is summarized in Supplementary Fig. S1. No formal risk-of-bias assessment was performed.

2. The testicular IL-18 system: basal biology and inflammatory regulation

2.1. Basal expression, regulation, and physiological context

IL-18 is synthesized as a precursor and is canonically processed by caspase-1, although alternative processing pathways have been described (Landy et al., 2024). Mature IL-18 signals through IL-18Rα/IL-18Rβ and activates MyD88-dependent pathways, including NF-κB and mitogen-activated protein kinase signaling (Tsutsumi et al., 2014; Novick, 2024). Its extracellular activity is regulated by IL-18-binding protein (IL-18BP), a high-affinity endogenous inhibitor of IL-18 (Landy et al., 2024; Novick, 2024). Thus, testicular IL-18 activity depends on processing, receptor availability, and the free IL-18/IL-18BP balance.

IL-18 signaling components are present in the testis. Full-length *IL18RAP*, which encodes IL-18Rβ, and an intron-retaining truncated transcript have been detected in human testis (Fiszer et al., 2007). Seminiferous tubules and testicular cell models respond to recombinant IL-18 (Strand et al., 2005; Inoue et al., 2020, 2023), although the distribution of functional IL-18Rα/IL-18Rβ complexes among testicular cell populations remains undefined.

Basal IL-18 expression is distributed across several testicular compartments and appears to vary with spermatogenic context (Table 1). In human testes, *IL18* transcripts and IL-18 immunoreactivity have been detected in germ-cell and somatic compartments, with prominent expression in germ-cell-enriched fractions and primary spermatocytes

Table 1
Basal, developmental, and contextual evidence relevant to the testicular IL-18 system.

Reference	Model and context	Key evidence	Key interpretive constraint
Human studies			
Rozwadowska et al., (2007)	Human testes with normal or impaired spermatogenesis; Leydig-cell-enriched and germ-cell-enriched fractions	qPCR detected *IL18*, *IL18R1*, and *IL18RAP* transcripts. *IL18* was highest in the germ-cell-enriched fraction, and IL-18-related transcripts tended to be lower in impaired spermatogenesis.	mRNA-only study; the germ-cell fraction contained mixed spermatocytes and round spermatids; pathological groups were heterogeneous.
Fiszer et al., (2007)	Human testicular interstitial and intratubular/germ-cell fractions from orchiectomy specimens	RT-PCR and sequencing identified full-length *IL18RAP* and an intron-4-retaining splice variant predicted to encode a truncated, putatively soluble protein.	Protein expression/secretion and IL-18 binding or regulatory function of the splice variant were not demonstrated; no inflammatory challenge was used.
Komsky et al., (2012)	Human NOA testes (n = 25) and fertile autopsy controls (n = 3) by IHC; FFPE samples described as normal (n = 5), SCOS (n = 6), or maturation arrest (n = 7) by RT-qPCR.	IL-18 immunoreactivity was detected in Sertoli, Leydig, and germ cells, with strongest staining in primary spermatocytes; *IL18* mRNA was lower in SCOS and maturation-arrest samples than in normal samples.	IHC and qPCR control sources were not fully reconciled; autopsy and TESE tissues may differ pre-analytically.
Mirghanizadeh Bafghi et al., (2024)	NOA (n = 30) and OA (n = 30): blood, testis, and seminal plasma; fertile normospermic controls (n = 30): blood only.	Testicular and blood *IL18* mRNA and seminal IL-18 were higher in NOA than OA; blood and testicular *IL18* expression were not significantly correlated.	No fertile testicular or seminal controls; single-center whole-tissue study; no mature/free IL-18 or cellular localization.
Mouse studies			
Abu Elhija et al., (2008b)	BALB/c mice; immature versus mature testes	IL-18, caspase-1/ICE, and IL-18Rα mRNA/protein were higher in immature testes; 24-kDa pro-IL-18 and an 18-kDa immunoreactive form were also more abundant.	Whole-testis developmental comparison; the 18-kDa form was interpreted as mature IL-18 based on molecular weight; ligand availability was not established.
Abu Elhija et al., (2008d)	BALB/c mice; immature versus mature testes and adult testicular sections	IL-18BP was constitutively detected in germ, Leydig/interstitial, and peritubular cells, with similar whole-testis expression in immature and mature mice.	Descriptive study; no isoform-specific analysis, free IL-18 measurement, or functional manipulation.
Rat study			
Strand et al., (2005)	Rat testes during postnatal development;	Pro-IL-18 localized mainly to meiotic/post-meiotic germ	Short-term, high-concentration ex vivo/in vitro rIL-

(*continued on next page*)

Table 1 (*continued*)

Reference	Model and context	Key evidence	Key interpretive constraint
	staged seminiferous tubules and Leydig-cell–enriched primary cultures (80–90% 3β-HSD-positive) exposed to rIL-18 ex vivo/in vitro	cells. rIL-18 (500 ng/mL) increased DNA synthesis in stage I tubules without apoptosis and did not significantly alter Leydig-cell proliferation or testosterone secretion.	18 exposure; four seminiferous stages were tested, but increased DNA synthesis was confined to stage I; no in vivo validation of the growth-associated response.

Abbreviations: FFPE, formalin-fixed paraffin-embedded; ICE, interleukin-1β-converting enzyme; IHC, immunohistochemistry; IL-18BP, interleukin-18-binding protein; IL-18R, interleukin-18 receptor; NOA, non-obstructive azoospermia; OA, obstructive azoospermia; qPCR, quantitative polymerase chain reaction; rIL-18, recombinant IL-18; RT-PCR, reverse-transcription polymerase chain reaction; RT-qPCR, reverse-transcription quantitative polymerase chain reaction; SCOS, Sertoli-cell-only syndrome; TESE, testicular sperm extraction; 3β-HSD, 3β-hydroxysteroid dehydrogenase.

(Rozwadowska et al., 2007; Komsky et al., 2012). Lower testicular *IL18* expression has been reported in some forms of impaired spermatogenesis (Rozwadowska et al., 2007; Komsky et al., 2012), whereas another study found higher *IL18* mRNA in non-obstructive than obstructive azoospermia (Mirghanizadeh Bafghi et al., 2024). These observations suggest that testicular IL-18 expression may reflect spermatogenic state and cellular composition rather than a simple relationship with spermatogenic function.

In rat testis, pro-IL-18 was expressed mainly in meiotic and post-meiotic germ cells, and recombinant IL-18 increased DNA synthesis in stage I seminiferous tubules without increasing apoptosis (Strand et al., 2005). This stage-restricted response supports local IL-18 responsiveness and a possible role in spermatogenic regulation, but does not establish endogenous IL-18 as a physiological germ-cell growth factor in vivo. In mice, expression of IL-18, caspase-1/ICE, and IL-18Rα differed between immature and mature testes, while IL-18BP was constitutively detected in germ-cell, Leydig/interstitial, and peritubular compartments (Abu Elhija et al., 2008b, 2008d). These findings support a pre-existing testicular IL-18 system whose baseline state varies with developmental and spermatogenic context.

2.2. Local and systemic contributions to testicular IL-18 during inflammation

During systemic inflammation, testicular IL-18 may derive from local production, the circulation, or both. The BTB separates the basal and adluminal compartments of the seminiferous epithelium but does not isolate the testicular interstitium from the circulation (Meinhardt and Hedger, 2011; Cheng and Mruk, 2012). Inflammatory signaling can modify Sertoli-cell junctional organization and BTB function (Zhang et al., 2014). The BTB does not preclude a systemic contribution to the testicular IL-18 environment, although access to seminiferous epithelial compartments has not been demonstrated.

Studies support local IL-18 production. LPS increased IL-18 secretion and expression in Leydig-cell–enriched primary murine cultures, although residual non-Leydig cells could not be excluded as a source (Abu Elhija et al., 2008a). In contrast, LPS did not increase endogenous IL-18 in TM3 Leydig cells, whereas IL-18 expression increased in RAW264.7 macrophages (Inoue et al., 2020). These findings suggest that inducible IL-18 production may differ among testicular and immune-cell contexts.

In vivo observations support inflammatory regulation of the testicular IL-18 system. Systemic LPS administration increased whole-testis IL-18 and altered caspase-1/ICE and IL-18Rα expression in adult mice, including an approximately 18-kDa immunoreactive IL-18 form consistent with mature IL-18 (Abu Elhija et al., 2008c; Table 2). By contrast, an 18-kDa testicular IL-18 form was not detected at the examined time point in a rat endotoxemia model (Strand et al., 2005). IL-18 abundance and processing may diverge across experimental conditions. Increased total testicular IL-18 cannot be assumed to reflect increased mature or bioavailable IL-18.

Circulating IL-18 may contribute to testicular exposure, as plasma IL-18 increases after LPS-induced endotoxemia (Inoue et al., 2015) and CLP-induced sepsis (Yamashita et al., 2017). Systemic LPS induces testicular NLRP3-dependent IL-1β production and neutrophil accumulation (Sano et al., 2022), demonstrating local inflammasome-associated responses without directly establishing IL-18 production. Testicular IL-18 exposure during systemic inflammation may reflect contributions from both the circulation and locally responsive testicular or immune cells. The key unresolved issue is how much circulating versus locally produced IL-18 contributes to bioavailable testicular IL-18 under defined inflammatory conditions.

3. Functional consequences of IL-18-associated responses in the testis

3.1. Germ-cell apoptosis across distinct inflammatory states

The principal in vivo functional evidence comes from global IL-18-knockout (KO) and wild-type (WT) mice examined in two endotoxemia settings (Inoue et al., 2015). In WT mice, the 12-h high-dose and 48-h lower-dose settings were operationally characterized as acute and recovery phases, respectively, based on systemic inflammatory and behavioral indices. Across these settings, global IL-18 deficiency was associated with opposite patterns of germ-cell apoptosis. During the acute setting, IL-18-KO mice showed less germ-cell apoptosis and reduced apoptosis-related signaling than WT mice, with molecular findings implicating death-receptor-, mitochondrial-, and nitric-oxide-associated pathways (Inoue et al., 2015). During the recovery setting, the relationship was reversed: IL-18-KO mice showed greater germ-cell apoptosis and focal germ-cell loss, accompanied by enhanced death-receptor-associated signaling (Inoue et al., 2015).

The reversal argues against a uniformly pro-apoptotic relationship between IL-18 and germ-cell survival during endotoxemia. These findings raise the possibility that IL-18 may promote germ-cell apoptosis in the acute setting but limit apoptosis during recovery. Global IL-18 deficiency can affect systemic inflammatory responses and therefore does not localize the responsible action to a particular testicular cell. Nevertheless, these experiments provide in vivo evidence that IL-18 status is associated with differential germ-cell apoptosis during systemic inflammation and support testing whether this functional relationship changes as inflammation evolves.

3.2. Leydig-cell responsiveness and potential steroidogenic implications

Leydig-cell dysfunction may provide a route by which systemic inflammation affects testicular endocrine function. LPS/Toll-like receptor 4 (TLR4) signaling suppressed basal and cAMP-stimulated testosterone production in primary mouse Leydig cells (Shang et al., 2011). Other testicular cell models showed altered steroidogenic and oxidative-stress pathways (Wang et al., 2020) or LPS-induced apoptosis in Leydig-cell–enriched rat cultures (Zhou et al., 2016). Inducible IL-18 production differed between Leydig-cell models (Abu Elhija et al., 2008a; Inoue et al., 2020), suggesting dependence on cellular composition and experimental context. Inflammatory Leydig-cell dysfunction can arise through multiple pathways, with IL-18 as a potential contributor.

LPS and recombinant IL-18 produced partly overlapping death-

Table 2
Experimental evidence under inflammatory conditions relevant to testicular IL-18 responses.

Reference	Model and context	Key evidence	Key interpretive constraint
Mouse in vivo studies			
Abu Elhija et al., (2008c)	Adult BALB/c mice; systemic LPS for 3 or 24 h	Testicular IL-18 concentration and *Il18* mRNA increased at 3 and 24 h after LPS. Increases in the 24- and 18-kDa immunoreactive IL-18 forms were demonstrated by western blot at 3 h; ICE and IL-18Rα transcripts showed dose- and time-dependent changes.	Whole-testis analysis did not identify the cellular source or target; free IL-18 was not measured; no IL-18-specific intervention.
Inoue et al., (2015)	Global IL-18-KO and WT mice; separate 12-h (40 mg/kg) and 48-h (20 mg/kg) LPS experiments.	IL-18-KO mice showed less germ-cell apoptosis at 12 h but greater apoptosis and focal germ-cell loss at 48 h.	Different LPS doses; global KO; systemic phases were defined in WT but not equivalently characterized in KO mice; no rescue, cell-specific manipulation, or fertility endpoint.
Rat in vivo study			
Strand et al., (2005)	Adult rats; systemic LPS for 6 h	Testicular pro-IL-18 remained detectable, but no 18-kDa immunoreactive form was detected at 6 h after systemic LPS.	Single 6-h time point; analysis focused on IL-18 processing and did not test IL-18-dependent testicular function in vivo.
Murine cell models			
Abu Elhija et al., (2008a)	Leydig-cell–enriched primary murine cultures (>90% 3β-HSD-positive) exposed to LPS for 3 or 24 h	LPS increased supernatant IL-18 at 3 and 24 h; increases in *Il18*, caspase-1/ICE, and IL-18Rα mRNA and in 24- and 18-kDa IL-18 immunoreactive forms were demonstrated at 3 h.	Residual non-Leydig sources cannot be excluded; maturation was inferred from molecular weight; free/bioactive IL-18 and the functional consequences of IL-18 induction were not established.
Inoue et al., (2020)	TM3 Leydig and RAW264.7 macrophage cell lines; LPS or rIL-18	LPS and rIL-18 produced partly overlapping death-receptor-related and caspase responses in TM3 cells. In TM3 cells, LPS decreased *Il18* mRNA at 6–12 h and did not increase IL-18 protein; in RAW264.7 cells, LPS increased *Il18* mRNA from 6 h and IL-18 protein from 12 h.	Immortalized cell lines; apoptosis-associated rIL-18 concentrations (10–100 ng/mL) were not benchmarked against local free IL-18 concentrations in vivo.
Inoue et al., (2023)	TM4 Sertoli cells exposed to LPS or rIL-18	LPS and rIL-18 elicited distinct transcriptional responses without detectable caspase-3 cleavage or reduced viability.	Immortalized cell line; no primary-cell, in vivo, or direct BTB functional validation.

Abbreviations: BTB, blood–testis barrier; ICE, interleukin-1β-converting enzyme; IL-18R, interleukin-18 receptor; KO, knockout; LPS, lipopolysaccharide; rIL-18, recombinant IL-18; WT, wild type; 3β-HSD, 3β-hydroxysteroid dehydrogenase.

receptor-associated apoptotic responses, including downstream caspase activation, while recombinant IL-18 induced inflammatory transcriptional responses (Inoue et al., 2020). Endogenous IL-18 production and responsiveness to IL-18 need not occur in parallel: Leydig cells may respond to IL-18 even under conditions in which they are not a major inducible source. Defining whether endogenous IL-18 contributes to Leydig-cell apoptosis in vivo and affects steroidogenesis will clarify its functional significance in Leydig-cell dysfunction.

3.3. *Sertoli-cell responses and barrier-related function*

Sertoli cells support germ-cell development, contribute to testicular immune regulation, and form the structural basis of the BTB (Meinhardt and Hedger, 2011; Cheng and Mruk, 2012). In TM4 Sertoli cells, neither LPS nor recombinant IL-18 induced detectable caspase-3 cleavage or loss of viability despite transcriptional responses to both stimuli, indicating a predominantly non-apoptotic response under these conditions (Inoue et al., 2023). This response differs from that observed in TM3 Leydig cells after recombinant IL-18 exposure, although the two cell types were examined in separate experiments (Inoue et al., 2020, 2023). Leydig and Sertoli cells may differ in their apoptotic sensitivity to inflammatory stimuli. The absence of overt apoptosis in TM4 cells does not establish preservation of Sertoli-cell function.

IL-6 can alter Sertoli-cell tight-junction integrity and BTB-protein localization without detectable caspase-3 activation (Zhang et al., 2014). Separate LPS studies have demonstrated disruption of tight-junction proteins and other BTB-related features in primary Sertoli-cell models (Feng et al., 2022; Zhu et al., 2022). Cell survival and barrier function are separable components of the Sertoli-cell inflammatory response. Direct assessment of IL-18 effects on Sertoli-cell junctional organization and BTB function is therefore needed to determine whether its non-apoptotic actions extend to barrier regulation.

4. Integrative interpretation: what does the evidence suggest about testicular IL-18?

Available studies suggest that apparently divergent IL-18-associated testicular responses may reflect differences in IL-18 exposure, inflammatory state, and cellular context rather than a uniform action of IL-18. The evidence also supports a pre-existing, inflammation-responsive testicular IL-18 system (Strand et al., 2005; Rozwadowska et al., 2007; Abu Elhija et al., 2008b–d; Komsky et al., 2012). The interpretation of IL-18 as a context-dependent modulator should therefore be regarded as a working model rather than an established mechanism. Total IL-18 abundance cannot be equated with bioavailable ligand, because processing and IL-18BP influence ligand availability for receptor signaling (Landy et al., 2024; Novick, 2024). A Leydig-cell–enriched primary culture supports local IL-18 inducibility, while plasma IL-18 increases after LPS-induced endotoxemia and CLP-induced sepsis; their relative contributions to testicular exposure remain unresolved (Abu Elhija et al., 2008a; Inoue et al., 2015; Yamashita et al., 2017).

Functional evidence suggests that IL-18-associated consequences vary with inflammatory and cellular context. Global IL-18 deficiency was associated with opposite germ-cell apoptosis patterns across distinct endotoxemia settings, raising the possibility that IL-18 may promote germ-cell apoptosis in the acute setting but limit it during recovery (Inoue et al., 2015). Because LPS dose and sampling time differed between the experiments, however, this reversal cannot be attributed specifically to the inflammatory phase. Recombinant IL-18 induced apoptosis-related responses in TM3 Leydig cells, whereas TM4 Sertoli cells remained viable despite transcriptional responsiveness (Inoue et al., 2020, 2023). These responses suggest that Leydig and Sertoli cells may differ in their apoptotic sensitivity to inflammatory stimuli. Inflammatory signals can alter Sertoli-cell junctional proteins and other BTB-related features (Feng et al., 2022; Zhu et al., 2022), while IL-6 can impair barrier-related function without detectable caspase-3 activation

(Zhang et al., 2014). Thus, IL-18-associated responses differ across germ-cell, Leydig-cell, and Sertoli-cell settings, and barrier dysfunction should be evaluated separately from apoptosis.

Overall, IL-18-associated testicular responses appear to vary across inflammatory and cellular contexts. These context-dependent patterns may reflect the interaction of a pre-existing local IL-18 system, inflammation-associated changes in local and circulating exposure, and the distinct properties of testicular cell populations. This working interpretation provides a rationale for testing whether IL-18 contributes to testicular injury or recovery. These findings and their interpretive limitations are summarized in Fig. 1.

5. Translational implications and research needs

Severe systemic inflammation also affects younger adults: adults aged 18–44 years accounted for 19.2% of the PROGRESS cohort, and 59.3% of the cohort was male, although the proportion of men within this age group was not reported (Beale et al., 2009). No human study identified in this review has directly linked systemic IL-18/IL-18BP dynamics during severe systemic inflammation with intratesticular IL-18 activity or reproductive outcomes. Nevertheless, human studies have established components of the IL-18 system within the testis (Rozwadowska et al., 2007; Fiszer et al., 2007; Komsky et al., 2012;

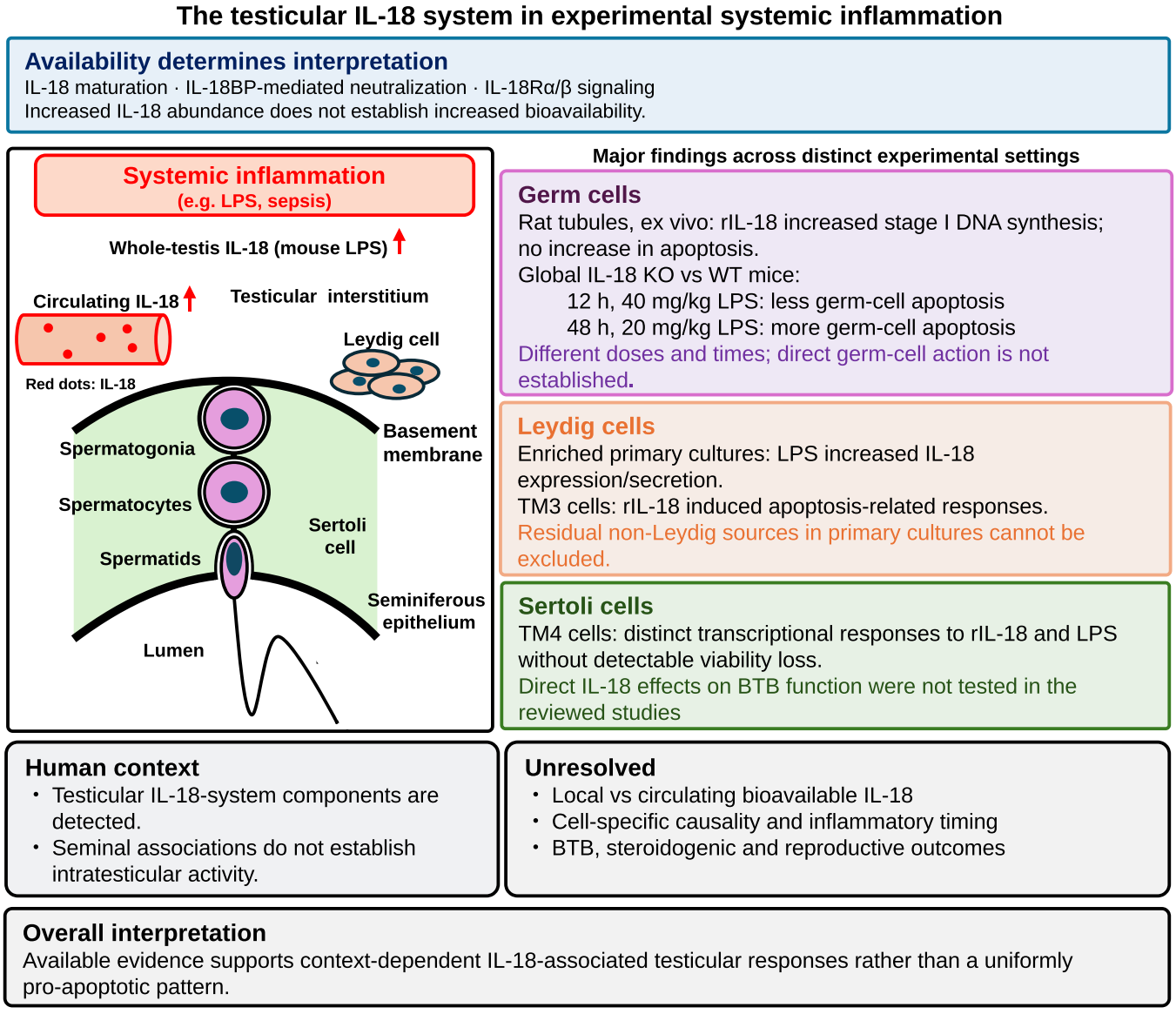

Fig. 1. The testicular IL-18 system in experimental systemic inflammation. Schematic overview of IL-18-associated findings across testicular compartments and distinct experimental settings. Increased circulating IL-18 has been reported in experimental inflammatory models, and increased whole-testis IL-18 abundance has been reported in a mouse systemic LPS model. The cellular panels summarize germ-cell DNA synthesis and apoptosis findings, LPS-induced IL-18 expression and secretion in Leydig-enriched primary cultures, and responses to recombinant IL-18 (rIL-18) and/or LPS in TM3 Leydig and TM4 Sertoli cell lines. These findings derive from different species, models, doses, and time points rather than a direct comparison across cell types. In particular, the germ-cell apoptosis findings in global IL-18-knockout mice derive from separate experiments using different LPS doses and sampling times. IL-18 maturation, IL-18BP-mediated neutralization, and receptor signaling provide the biological framework for interpreting these findings. The anatomical schematic illustrates the major testicular compartments; the sources of bioavailable IL-18 and cell-specific causal mechanisms in vivo remain unresolved. Human testicular and seminal findings provide additional translational context. Upward arrows indicate reported increases under the specified experimental conditions. Red dots schematically represent circulating IL-18; no route of transfer into the testis is implied. The schematic is not to scale. Abbreviations: BTB, blood–testis barrier; IL-18, interleukin-18; IL-18BP, interleukin-18-binding protein; IL-18Rα/β, IL-18 receptor α/β chains; KO, knockout; LPS, lipopolysaccharide; rIL-18, recombinant IL-18; TM3 and TM4, mouse Leydig- and Sertoli-cell lines, respectively; WT, wild type.

Mirghanizadeh Bafghi et al., 2024). Human seminal IL-18 studies have reported context-specific associations with genital-tract inflammation, semen characteristics, or sperm DNA fragmentation (Matalliotakis et al., 2006; Ejehi et al., 2026; Supplementary Table S1). Separate ART studies have examined associations with fertilization or pregnancy-related outcomes (Nikolaeva et al., 2016; Amor et al., 2025; Supplementary Table S2). However, in the 2026 systematic review, IL-18 data were insufficient for quantitative meta-analysis, and all four included studies reported no significant overall difference between infertile and control groups; an increase was confined to an infection-defined subgroup in one study (Lyons et al., 2026). Seminal IL-18 should be treated as an exploratory measure rather than a validated biomarker of fertility status or a surrogate for intratesticular IL-18 activity. One translational need is a longitudinal study of men with severe systemic inflammation followed through recovery, with serial measurement of circulating IL-18 and IL-18BP, reproductive hormones, and semen parameters; seminal IL-18 could be included as an exploratory measure of the reproductive-tract milieu. Such studies would test whether systemic IL-18 dynamics are associated with reproductive changes.

Another need is to test whether IL-18–injury associations in the testis change as inflammation evolves. The contrasting germ-cell apoptosis patterns in global IL-18-deficient mice provide a biological rationale for testing IL-18 function at defined stages of inflammation (Inoue et al., 2015). Time-restricted modulation of the IL-18/IL-18BP system after inflammatory challenge, combined with matched measurements of systemic and testicular inflammation, apoptosis, steroidogenesis, BTB integrity, spermatogenic recovery, and sperm function, could distinguish effects during injury and recovery from those of constitutive global deficiency. Although not reproductive-system specific, human data linked an IL-18-associated monocyte program to postoperative recovery (Papatheodorou et al., 2025). In an independent small sepsis cohort, an IL-18-related cytokine ratio was associated with SOFA-defined severity (Papatheodorou et al., 2025). These indirect observations support a time-resolved study design but do not establish a testicular role for IL-18.

A further need is to define how systemic and local IL-18 signals reach testicular compartments. Spatial and single-cell approaches could identify inducible IL-18-producing populations, while cell-specific manipulation of *Il18* in candidate source cells and *Il18r1* or *Il18rap* in candidate responder cells could distinguish systemic from local testicular signaling. Rescue, neutralization, primary-cell, and organotypic experiments could establish how IL-18-related responses observed in germ-cell, Leydig-cell, and Sertoli-cell settings translate to intact testicular tissue (Abu Elhija et al., 2008a; Inoue et al., 2015, 2020, 2023).

Across these needs, polymicrobial sepsis models could test whether findings from LPS endotoxemia extend to systemic infection. Testosterone production, spermatogenic recovery, sperm number and function, and BTB integrity represent proximal outcomes, while fertility can serve as a downstream endpoint. Because several functional observations derive from studies by the present authors, independent replication across laboratories and inflammatory models would strengthen the evidence base. These approaches could establish whether the IL-18/IL-18BP system has value in inflammation-associated male reproductive dysfunction.

6. Conclusion

Current evidence supports IL-18 as a constitutive and inflammation-responsive component of the testicular environment whose associated responses are not uniformly pro-apoptotic. During systemic inflammation, testicular IL-18 exposure may reflect both local production and circulating IL-18, although their relative contributions remain unresolved. Functional responses also differ across germ-cell, Leydig-cell, and Sertoli-cell settings. The contrasting germ-cell apoptosis patterns observed across distinct endotoxemia settings, together with apoptosis-related responses in the TM3 Leydig cell line and non-apoptotic transcriptional responsiveness in the TM4 Sertoli cell line, suggest that the biological consequences associated with IL-18 depend on inflammatory and cellular context. These findings provide a basis for testing whether and how IL-18 contributes to testicular injury and recovery through temporally controlled and cell-specific approaches. Longitudinal studies in men with severe systemic inflammation are needed to determine whether IL-18/IL-18BP has clinical value for reproductive monitoring.

CRediT authorship contribution statement

Taketo Inoue: Writing – original draft, Conceptualization. **Michiko Aoyama-Ishikawa:** Writing – review & editing. **Mikiko Uemura:** Writing – review & editing.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT (OpenAI) for English-language editing and manuscript/source consistency checks. The authors reviewed and verified all AI-assisted output and take full responsibility for the content of the article.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jri.2026.105164.

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