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评 述
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睾丸免疫调节与睾丸炎: Tyro3/Axl/Mer 受体酪氨酸激酶与模式识别受体的功能

江倩, 赵祥, 薛社普, 韩代书*

北京协和医学院基础学院, 中国医学科学院基础医学研究所, 北京 100005
* 联系人, E-mail: dshan@ibms.pumc.edu.cn

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摘要 哺乳动物睾丸具有特殊的免疫环境来维持睾丸功能. 睾丸细胞分泌多种免疫调节因子, 参与调节睾丸免疫环境, 免疫豁免与睾丸固有免疫应答可防止自身免疫反应及抵御微生物感染. 当睾丸免疫平衡被破坏时, 会引起睾丸炎, 干扰精子发生, 并可导致不育. 多种免疫调控机制共同维持睾丸免疫平衡. 近年来发现, Tyro3/Axl/Mer (TAM)受体酪氨酸激酶与模式识别受体在调节睾丸免疫环境中发挥重要作用, 本文将综述相关的研究进展, 提出有待深入研究的方向.

关键词 睾丸免疫, Tyro3/Axl/Mer 受体, 模式识别受体, 睾丸炎, 男性不育

不孕不育已成为严重影响人类的公共健康问题, 由微生物感染、环境毒素、组织损伤等因素引起的生殖系统免疫反应是不孕不育的重要病因, 其中, 睾丸炎可以导致男性不育[1]. 精子发生完成于机体免疫耐受机制建立以后, 生精细胞产生大量具有免疫原性的分子. 然而在生理条件下, 生殖细胞在睾丸中并不诱导免疫反应, 这是由于睾丸具有免疫豁免环境[2]. 另一方面, 睾丸可以被多种微生物(病毒、细菌、寄生虫)感染, 为了克服免疫豁免环境, 抵御入侵的病原体, 睾丸建立了有效的固有防御能力[3]. 深入认识睾丸免疫调节机制, 不仅可为防治免疫相关的男性不育提供线索, 而且可能为预防移植器官的免疫排斥及诱导组织特异的防御能力提供思路. 近10年来, 本研究组[4]用小鼠(*Mus musculus*)为模型, 研究睾丸免疫调节机制, 揭示了TAM受体对睾丸免疫豁免的调节作用[5]以及模式识别受体(pattern recognition receptors, PRR)启动的睾丸细胞固有免疫应答[6]. 本文重点综述TAM受体与PRR在调节睾丸免疫环境中的功能.

1 睾丸免疫环境

哺乳动物睾丸具有复杂的组织结构, 以适应其生理功能. 从解剖学上, 睾丸与机体相对分离, 器官温度明显低于正常体温. 为了防止产生自身免疫反应, 并且有效抵御微生物病原体, 睾丸建立了特殊的免疫环境.

1.1 睾丸细胞类型

睾丸组织可分为曲细精管及间质两部分, 由多种细胞组成(图1). 管周肌样细胞形成曲细精管壁, 管内由Sertoli细胞与生精细胞组成. 生精细胞按照不同分化阶段有序地排列于两Sertoli细胞之间, 被Sertoli细胞紧密包裹, 形成生精上皮, 为精子发生的场所. 相邻Sertoli细胞在靠近管壁处形成了一个特殊

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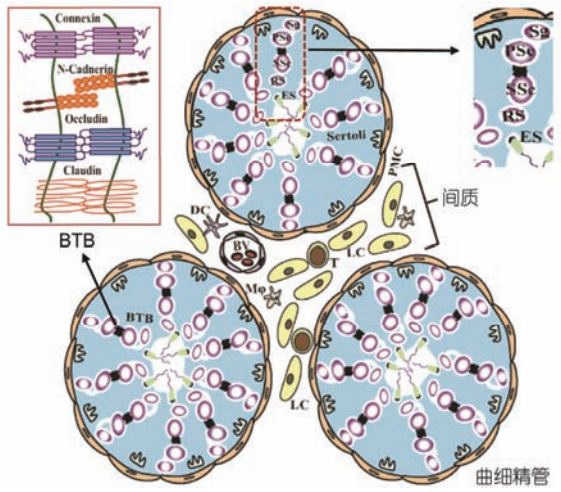

图 1 (网络版彩色)睾丸组织结构示意图. 睾丸组织由曲细精管与间质两部分组成: 曲细精管是精子发生的场所, 管壁由管周肌样细胞(peritubular myoid cells, PMC)组成, Sertoli细胞包裹不同分化阶段的生精细胞. 生精细胞包括精原细胞(spermatogonia, Sg), 初级精母细胞(primary spermatocytes, PSc), 次级精母细胞(secondary spermatocytes, SSc), 圆形精子细胞(round spermatids, RS)与长形精子细胞(elongating spermatids, ES). 相邻Sertoli细胞在靠近曲细精管基底部由多种黏附分子形成血/睾屏障(BTB). 睾丸间质主要由Leydig细胞与一些免疫细胞组成. 包括巨噬细胞(macrophages, Mφ)、T淋巴细胞(T lymphocytes, T)、树突状细胞(dendritic cells, DC)与血管(blood vessels, BV)

Figure 1 (Color online) Testicular structure. The testis is constituted of seminiferous tubules and interstitial spaces. Spermatogenesis occurs within the seminiferous tubules, which are formed by peritubular myoid cells (PMC), Sertoli cells and different stages of spermatogenic cells. Spermatogenic cells include spermatogonia (Sg), primary spermatocytes (PSc), secondary spermatocytes (SSc), round spermatids (RS) and elongating spermatids (ES). The blood-testis barrier (BTB) is formed by several adhesion molecules between two Sertoli cells near the basal membrane of the Seminiferous tubules. The interstitial spaces are composed of Leydig cells and certain immune cells, including macrophages (Mφ), T lymphocytes (T) and dendritic cells (DC). Blood vessels (BV) are also located in the interstitial spaces

的结构, 称之为血-睾屏障(blood-testis barrier, BTB), 将生精上皮分为基底与管腔两部分. BTB可以限制细胞与大分子物质通过, 是隔离免疫细胞与自身抗原、防止自身免疫反应的重要机制. 睾丸间质主要由Leydig细胞组成, Leydig细胞合成雄激素. 间质中还有多种免疫细胞, 主要为巨噬细胞, 可能是睾丸抵御病原体感染的重要防线. 此外, 还有少量的T淋巴细胞、树突状细胞及肥大细胞, 这些免疫细胞参与调节多种睾丸病理生理过程[7].

1.2 睾丸免疫特征

睾丸免疫特征表现为两方面: 免疫豁免环境与固有免疫防御[3]. 睾丸免疫豁免是指系统性的免疫反应受到明显抑制, 防止生殖细胞诱导免疫反应. 组织结构、免疫抑制因子以及免疫耐受共同调节睾丸免疫豁免环境. BTB是重要的结构基础, 可以将曲细精管内的大部分生精细胞抗原与间质中的免疫组分隔离, 如果BTB受到破坏, 可引起自身免疫反应. 然而睾丸间质也表现出免疫豁免特性, 外来组织移植物可在睾丸间质中逃避免疫排斥, 多种免疫抑制因子参与抑制睾丸间质中的免疫反应. 此外, 虽然精子发生完成于免疫耐受建立以后, 免疫系统对生精细胞抗原仍具有一定的耐受能力, 因为生殖细胞自身抗原不能单独诱导自身免疫疾病, 需要有佐剂才能诱导自身免疫睾丸炎. 近来发现TAM受体家族可以抑制睾丸局部免疫反应与调节系统性免疫耐受.

虽然睾丸是一个免疫豁免位点, 也是一个容易受到多种微生物感染的器官. 感染的病原体通常能被有效清除, 说明睾丸存在着免疫系统外的防御能力. 睾丸细胞中PRR的发现揭示了睾丸特异的防御机制, 发现多数睾丸组织特异细胞(包括Sertoli, Leydig与生殖细胞)表达丰富的PRR, 并能被其配体激活, 启动抵御微生物的固有免疫应答.

2 TAM受体调节睾丸免疫

2.1 TAM受体及其配体

TAM受体属于一类跨膜受体酪氨酸激酶亚家族, 包括Tyro3, Axl和Mer (TAM) 3个成员, 它们具有相似的结构(图2): 胞外区包含两个免疫球蛋白样(immunoglobulin, Ig)结构域和两个纤维黏连蛋白Ⅲ(fibronectin type Ⅲ, FN Ⅲ)重复序列, 跨膜结构域与胞内酪氨酸蛋白激酶(tyrosine kinase, TK)结构域. 生长停滞特异性基因6 (growth arrest-specific gene 6, Gas6)和Protein S (ProS)是TAM受体家族的共同配体, 其结构包括一个氨基(N)端谷氨酸(glutamic acid, Gla)结构域, 4个表皮生长因子(epidermal growth factor, EGF)样结构域和一个羟基(C)端性激素结合球蛋白(sex hormone binding globulin, SHBG)结构域. TAM受体的Ig结构域与Gas6和ProS的SHBG结合, 激活TK启动胞质信号通路, 进而调节细胞增殖, 天然免疫与吞噬凋亡细胞[8,9].

2.2 TAM受体在睾丸中的功能

首先发现TAM/Gas6在小鼠睾丸中表达水平

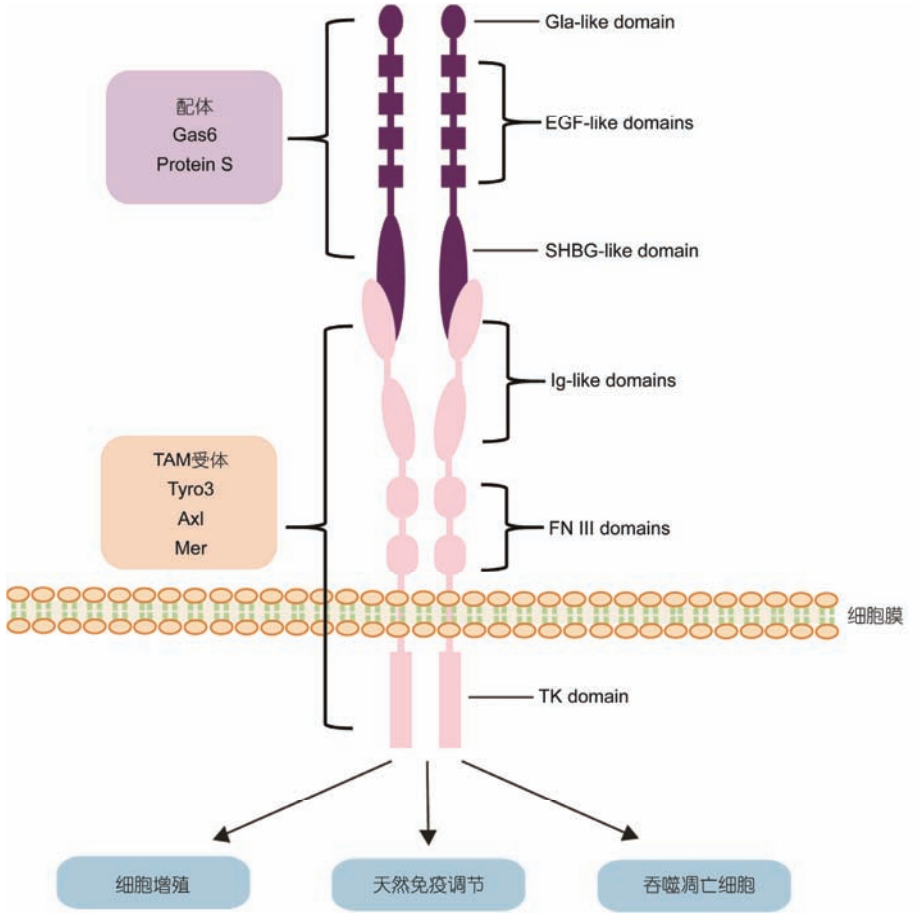

图 2 (网络版彩色) TAM受体及其配体示意图. TAM受体包含 3 个成员: Tyro3, Axl和Mer, 它们具有相似的结构, Gas6 和ProS是TAM受体家族的共同配体. TAM受体N端胞外区的Ig样结构域与Gas6 和ProS的C端结合, 激活胞内区的TK活性, 启动胞内信号通路, 调节多种生物学功能, 包括细胞增殖、天然免疫反应及吞噬凋亡细胞

Figure 2 (Color online) TAM receptors and ligands. TAM receptors contain three members: Tyro3, Axl and Mer. They possess similar structure. Gas6 and ProS are common ligands of TAM receptors. Ig-like domains at extracellular N-terminal of TAM receptors bind to C-terminal of Gas6 and ProS, thus activating TK and initiating intracellular signaling pathways. TAM signaling regulates various biological functions, including cell proliferation, innate immune response, and phagocytosis of apoptotic cells

很高[10]. 3个TAM受体均在Sertoli细胞中表达, Axl和Mer也表达于Leydig细胞, 而Gas6只在Leydig细胞中表达, 但生精细胞并不表达TAM与Gas6. 值得关注的是: TAM基因敲除($TAM^{-/-}$)小鼠为雄性不育, 出生5周后精子发生出现异常, 随着鼠龄的增长, 生精细胞逐渐退化[11], 但$TAM^{-/-}$小鼠中的睾丸可以正常合成睾酮, 这说明TAM受体主要通过作用于Sertoli细胞来调节精子发生(图3).

2.3 TAM受体调节Sertoli细胞的吞噬功能

Sertoli细胞组成了精子发生的微环境, 为生精细胞提供营养, 并吞噬清除残体与凋亡的生精细胞, Sertoli细胞的吞噬功能在维持曲细精管稳态和正常精子发生中具有重要意义[12]. TAM可以介导Sertoli细胞吞噬清除凋亡细胞, 其中Axl和Tyro3主要负责识别与结合凋亡细胞, 而Mer则启动吞噬信号[13]. 在正常精子发生过程中, 约有75%的生精细胞发生凋亡[14], 而且精子发生后期, 大部分胞质成分脱落, 形成残体. 凋亡的生精细胞及残体被Sertoli细胞吞噬后被重复利用, 可作为Sertoli细胞的能源(图3)[15]. 另外, 吞噬凋亡细胞是清除内源性抗原的重要机制, 可避免产生自身免疫反应[16]. 当机体的细胞吞噬功能发生障碍时, 凋亡细胞裂解, 释放出自身抗原, 诱导自身免疫性疾病[17]. 许多生精细胞与残体中的抗原可诱导自身免疫反应[18], Sertoli细胞及时吞噬残体与凋亡生精细胞可清除自身抗原, 避免自身免疫反

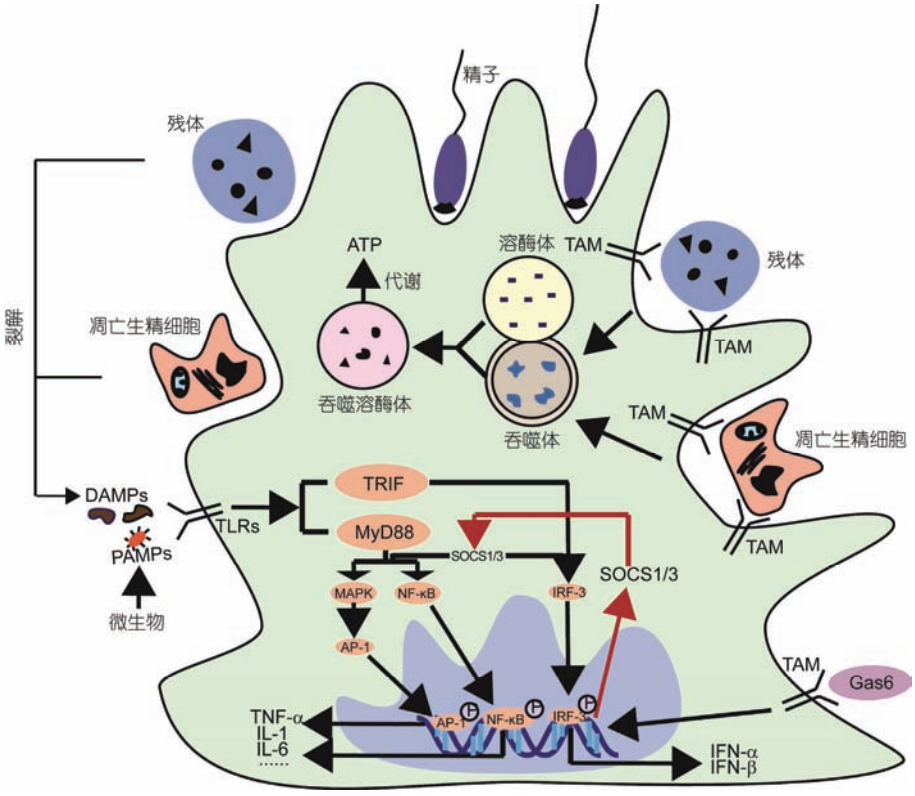

图 3 (网络版彩色) TAM受体在Sertoli细胞中的功能. TAM受体在Sertoli细胞中具有两方面的功能: (ⅰ) 促进Sertoli细胞吞噬凋亡生精细胞与残体, 并且可以被重复利用作为细胞能源. (ⅱ) TAM抑制Toll-样受体(TLR)信号通路, TAM被Gas6 激活后可诱导Sertoli细胞表达细胞因子信号传导抑制蛋白 1/3 (suppressor of cytokine signaling1/3, SOCS1/3), SOCS1/3 抑制髓系分化因子 88 (myeloid differentiation factor 88, MyD88)与含有TIR结构能诱导干扰素 β 的接头分子(TIR domian-containing adaptor inducing interferon beta，TRIF)介导的信号通路

Figure 3 (Color online) Role of TAM receptors in Sertoli cells. TAM receptors play two functions in Sertoli cells: (ⅰ) TAM receptors facilitate phagocytosis of apoptotic germ cells and residual bodies by Sertoli cells, which can be recycled as energy sources. (ⅱ) TAM negatively regulate Toll-like receptor (TLR) signaling. TAM signaling induces expression of suppressor of cytokine signaling 1/3 (SOCS1/3), which inhibit MyD88-and TRIF-dependent signaling pathways

应. Sertoli细胞的吞噬功能缺陷可诱发自身免疫性睾丸炎[19], 这可能是*TAM*$^{-/-}$小鼠产生睾丸炎的机制[20]. 因此, TAM受体可促进Sertoli细胞的吞噬功能, 从而避免生精细胞诱导自身免疫反应.

2.4 TAM/Gas6系统抑制睾丸细胞的固有免疫应答

睾丸为了克服免疫豁免环境, 有效抵御微生物感染, 多数睾丸细胞具备固有防御机制, 近年来本研究组[3]对PRR启动的睾丸细胞固有免疫应答进行了广泛的研究. 多种Toll样受体(Toll-like receptors, TLR)在Sertoli, Leydig与生殖细胞中表达, 并启动睾丸细胞的固有免疫应答[21]. 然而, TLR启动的固有免疫应答必须受到严格调控, 因为过度反应会产生大量炎症因子, 损伤组织功能. 发现TAM/Gas6系统通过抑制Sertoli细胞中TLR信号通路(图3), 降低炎症因子表达水平[22]. 除了Sertoli细胞, TAM/Gas6系统也抑制Leydig细胞中的TLR信号通路[23], 表明TAM/Gas6系统在维持睾丸免疫稳态中行使重要功能. 与此相符, *TAM*$^{-/-}$小鼠睾丸免疫豁免受到破坏, 睾丸组织中出现了巨噬细胞和淋巴细胞的浸润; 主要炎症因子, 包括肿瘤坏死因子-α (tumour necrosis factor-α, TNF-α)、白介素-6 (interleukin-6, IL-6)以及单核细胞趋化因子-1 (monocyte chemotactic protein-1, MCP-1)的表达量升高; BTB受损; 并产生自身抗体, 发展为自身免疫性睾丸炎[20]. 值得注意的是, *TAM*$^{-/-}$小鼠的自身免疫性睾丸炎发生在成年之后, 此时生精细胞产生大量残体, 凋亡的生精细胞也比较多. 鉴于*TAM*$^{-/-}$ Sertoli细胞吞噬能力降低, 不能被及时清除的残体与凋亡细胞可释放内源性配体, 激活Sertoli细胞中的TLR, 诱导产生炎症反应[24]. 因此, TAM/

Gas6系统可以抑制睾丸细胞中TLR启动的固有免疫应答, 从而维持睾丸免疫稳态.

2.5 TAM受体调节生精细胞的免疫耐受

除了局部免疫抑制机制, 对自身抗原的免疫耐受也调节睾丸免疫豁免, TAM受体有助于免疫系统对生精细胞自身抗原的耐受. 与*TAM*$^{-/-}$小鼠不同, *Axl*和*Mer*双基因敲除(*AM*$^{-/-}$)小鼠可以正常生育, 并不自发产生自身免疫性睾丸炎[20]. 然而, *AM*$^{-/-}$小鼠对实验性自身免疫性睾丸炎(experimental autoimmune orchitis, EAO)比较敏感, 表明Axl和Mer参与调节生精细胞的免疫耐受[25]. 利用生精细胞抗原免疫啮齿类动物, 可诱导产生EAO, 用来研究自身免疫性睾丸炎的病理机制[26]. 利用生精细胞抗原一次性免疫*AM*$^{-/-}$小鼠即可诱导严重的EAO, 表现为巨噬细胞和T淋巴细胞浸润, 精子发生受阻, BTB受损, 并产生自身抗体[25]. 对*Axl*$^{-/-}$或*Mer*$^{-/-}$小鼠进行相同免疫, 只产生轻度EAO, 一次免疫野生小鼠不能诱导EAO. 这些结果表明, Axl和Mer可以协同调节免疫系统对生精细胞自身抗原的耐受. 与此相符, Axl和Mer在抗原递呈细胞(树突状细胞和巨噬细胞)中表达[27]. 对于Axl和Mer调节生殖细胞的免疫耐受机制值得深入研究, 可进一步揭示系统性免疫耐受在维持睾丸免疫豁免中的功能.

2.6 自身免疫睾丸炎

自身免疫睾丸炎是一种慢性炎症, 可导致男性不育, 其病理机制利用EAO模型进行了广泛的研究[26]. EAO表现为免疫细胞浸润和生殖细胞退化, 浸润的免疫细胞主要为巨噬细胞, 巨噬细胞会分泌大量的炎症因子, 包括TNF-α和IL-6, 这些因子可诱导生殖细胞的凋亡[28,29]. EAO也可抑制睾酮合成, 诱导抗生精细胞的自身抗体产生, 从而干扰男性生育能力. 虽然抗精子抗体是临床上男性不育的病因之一, 但自身免疫性睾丸炎在人类中很少见, 可能是由于缺乏精确的诊断指标而低估了这一疾病的发生率. 鉴定自身免疫睾丸炎中特异性自身抗体, 可以促进这一疾病的诊断, 有关实验室正在开展这方面的研究.

3 PRR启动的睾丸细胞固有免疫应答

固有免疫系统利用PRR感知微生物, 启动免疫应答来抵御微生物感染. PRR属于一类受体家族, 可以识别微生物的保守成分: 病原相关模式分子(pathogen-associated molecular pattern, PAMP). PRR被PAMP激活后, 启动固有免疫应答, 并可调节获得性免疫, 是抵抗微生物感染的关键机制[30]. 目前已经发现多个PRR亚家族, 研究比较多的包括TLR、视黄酸诱导基因Ⅰ(retinoic acid-inducible gene Ⅰ, RIG-Ⅰ)样受体(RIG-Ⅰ-like receptor, RLR)以及DNA感受器[31], PRR可启动不同的信号通路(图4).

在哺乳动物中, 已经发现13种TLR成员, 它们属于跨膜蛋白, 位于细胞膜或内吞体膜上. TLR可以识别多种微生物(包括细菌、病毒以及寄生虫)的PAMP. TLR信号通路通过激活核因子κB (nuclear factor kappa B, NF-κB)、激活蛋白-1 (activate protein-1, AP-1)和干扰素调节因子(interferon regulatory factor, IRF)诱导炎症因子和1型干扰素(interferons, IFN-α与IFN-β)的产生. RLR家族包括RIG-Ⅰ和黑色素瘤分化相关抗原5 (melanoma differentiation-associated antigen 5, MDA5)两个成员. RIG-I和MDA5可以识别病毒的双链RNA (dsRNA), 并通过激活干扰素β启动子刺激因子-1 (IFN-β promoter stimulator-1, IPS-1)诱导固有抗病毒反应[32]. 近年来, 发现了多种细胞内DNA感受器, 包括p204, cGMP-AMP合酶等, 它们可以识别病毒和细菌DNA, 通过干扰素基因刺激蛋白(stimulator of IFN gene, STING)信号通路启动固有免疫应答[33]. IPS-1和STING通路激活IRF3, 诱导1型干扰素的表达, IFN-α和IFN-β进而诱导表达多种抗病毒蛋白, 这些抗病毒蛋白可以通过不同的机制抵御入侵的病毒, 是固有抗病毒反应的重要机制[34].

3.1 TLR在Sertoli细胞中的功能

睾丸中的TLR最初是在小鼠Sertoli细胞中发现的. Riccioli等人[35]首先在小鼠Sertoli细胞表达*TLR2*, *TLR4*, *TLR5*与*TLR6*的mRNA, 并对TLR2与TLR5的功能进行了研究. 发现TLR2与TLR5的配体可激活NF-κB, 诱导趋化因子MCP-1与黏附蛋白ICAM-1在Sertoli细胞中表达. 随后在RNA与蛋白水平证实小鼠Sertoli细胞表达TLR2, TLR3, TLR4与TLR5[23], 这些TLR可被相应的配体激活, 进而活化NF-κB. TLR3与TLR4被激活后可诱导Sertoli细胞表达IL-1, IL-6, IFN-α与IFN-β, 而TLR2与TLR5信号通路可诱导IL-1与IL-6, 但不显著影响IFN-α与IFN-β. 同时另一研究也证实TLR3在小鼠Sertoli细胞中可以启动固有抗病毒反应与炎症反应, 诱导MCP-1, ICAM-1, IFN-α与IFN-β

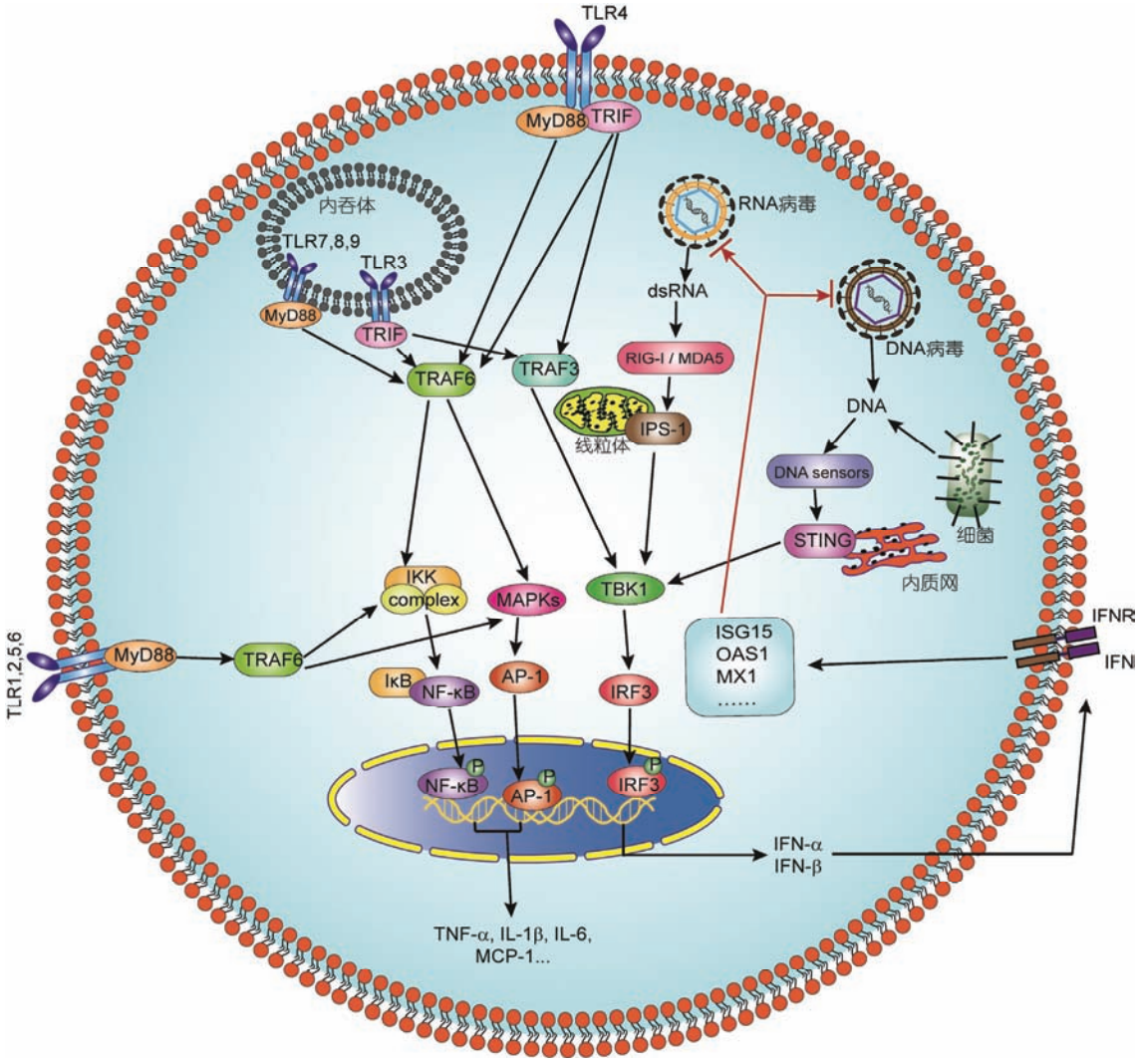

图 4 (网络版彩色) PRR信号通路. 研究比较清楚的 3 类PRR包括: TLR, RLR (RIG-I/MDA5)与DNA感受器. TLR位于细胞膜与内吞体膜上, 激活后启动MyD88 或TRIF信号通路, 通过激活NF-κB, AP-1 或IRF3 诱导表达免疫调节分子(包括炎症因子、趋化因子及干扰素). RLR与DNA感受器位于细胞质中, 识别病原体的dsRNA与DNA成分, 分别通过接头分子IPS-1 与STING启动信号通路, 主要诱导 1 型干扰素(IFN-α与IFN-β), IFN可诱导细胞表达抗病毒蛋白, 抵御入侵的病毒

Figure 4 (Color online) PRR signaling pathways. TLR, RLR (RIG-I/MDA5) and DNA sensors are three well-known PRR families. TLR are located on cellular and endosomal membranes. TLR initiate MyD88- or TRIF-dependent signaling pathways, thereby inducing the expression of pro-inflammatory cytokines, chemokines and interferons through the activation of NF-κB, AP-1 or IRF3. RLR and DNA sensors are located in cytoplasm. These cytosolic PRR recognize dsRNA and DNA of pathogens and induce type 1 IFNs (IFN-α and IFN-β) through IPS-1- and STING-dependent signaling pathways. Type 1 IFNs induce antiviral protein expression in infected cells to counteract invading viruses

的表达[36]. 这些结果说明, Sertoli细胞具有抵抗微生物感染的固有防御能力, 可能是睾丸克服免疫豁免环境, 抵御病原体的机制. 除了TLR外, 其他PRR在Sertoli细胞中的功能有待研究. 近来发现其他睾丸细胞(包括Leydig与生殖细胞)也具有固有防御能力.

3.2 PRR在Leydig细胞中的功能

TLR3和TLR4在小鼠Leydig细胞中表达[23], 并可以被其配体激活, 诱导表达炎症因子和1型干扰素. 而且, TLR3和TLR4的激活抑制雄激素合成, 可能是炎症因子的作用, 因为IL-1与TNF-α可抑制睾酮合成[37,38]. 值得注意的是, Leydig细胞中TLR信号通路可被Axl与Mer受体抑制, 可以避免高水平的炎症因子损伤睾丸功能, 并有利于维持免疫豁免环境[23].

除了TLR外, 小鼠Leydig细胞还表达RIG-Ⅰ和MDA5, 从而识别dsRNA, 启动IPS-1信号通路, 介导

固有抗病毒反应[39]. Leydig细胞中IPS-1信号通路可激活NF-κB与IRF3, 诱导表达炎症因子和1型干扰素. 此外, dsRNA刺激小鼠Leydig细胞后, 可以促进表达一些抗病毒蛋白, 包括干扰素刺激基因15 (interferon stimulating gene 15, ISG15)、寡腺苷酸合成酶1 (oligoadenylate synthetase 1, OAS1)、MX尿苷三磷酸酶1 (MX GTPase 1, MX1). ISG15可以放大细胞的抗病毒信号通路, OAS1降解病毒RNA, 而MX1则可抑制病毒转录, 共同抵御侵入细胞的病毒[34]. 此外, dsRNA也能抑制其睾酮合成, 表明RNA感受器启动的固有抗病毒反应可以干扰睾丸的内分泌功能[39].

p204是小鼠细胞中的一种DNA感受器, 与其接头分子STING在小鼠Leydig细胞中表达[40]. p204启动STING信号通路, 诱导1型干扰素的产生, 进而诱导Leydig细胞表达ISG15, OAS1和MX1. 值得关注的是, 在Leydig细胞中p204启动的固有抗病毒反应并不显著诱导炎症因子, 也不抑制睾酮合成. 这可能是RNA病毒比DNA病毒更容易诱导睾丸炎并损伤男性生育的原因[41,42]. 因此, 诱导Leydig细胞中DNA感受器信号通路是抵御病毒感染及维持睾丸正常功能的理想策略.

3.3 生精细胞中的PRR

成年睾丸中, 90%以上的睾丸细胞为生精细胞. 这些生精细胞可受到来自血液循环及下游生殖管道微生物的感染, 有理由推测, 生殖细胞也可能参与防御微生物感染. 发现TLR3在小鼠精母细胞和精原细胞中表达, dsRNA通过TLR3激活NF-κB, 从而诱导这些生精细胞产生IL-1β, IL-6和TNF-α, dsRNA也可以诱导生精细胞表达IFN-α, IFN-β, OAS1和MX1[43]. 由于精原细胞和精母细胞分别位于BTB两侧, 所以TLR3启动的抗病毒应答可能参与曲细精管抵御来自血液循环与生殖管道的病毒感染. 圆形精子表达MDA5, dsRNA通过激活MDA5信号通路诱导圆形精子细胞固有抗病毒反应[39].

刚地弓形虫(*Toxoplasma gondii*)与尿道致病性大肠杆菌(*uropathogenic Escherichia coli*, UPEC)可以通过下游生殖管道感染睾丸, 损伤精子发生[44,45]. 发现小鼠圆形精子细胞表达TLR11, 并可以被*T. gondii*与UPEC激活, 启动圆形精子的固有免疫应答[46]. *T. gondii*可诱导生精细胞表达MCP-1, IL-12和IFN-γ, 而UPEC则诱导TNF-α, IL-6和IL-1β, 表明生殖细胞具有抵御*T. gondii*和UPEC的能力. 然而TLR11在人类没有功能[47], 这可能是*T. gondii*和UPEC主要在人体致病的原因. 成年睾丸的大部分细胞为生精细胞, 而且主要位于BTB的内侧, 与免疫系统分离, 因此, 生精细胞抵御微生物的功能值得特别关注. 实际上很少微生物病原体可以感染生精细胞, 可能因为这些细胞具有较强的固有防御能力. 然而, 与Sertoli和Leydig细胞相比, 生精细胞表达较少的PRR, 而且固有免疫应答水平也较低. 生精细胞是否存在其他机制来抵御微生物病原体, 值得深入研究.

3.4 睾丸炎

尽管睾丸是一个免疫豁免位点, 但多种微生物(包括细菌、病毒与寄生虫)可感染睾丸, 并诱发睾丸炎. 常见的两种性传播细菌: 淋病奈瑟菌(*Neisseria gonorrhoeae*)和沙眼衣原体(*Chlamydia trachomatis*), 感染生殖道后可引起睾丸炎和附睾炎[48]. 腹腔注射大肠杆菌脂多糖可抑制大鼠睾酮合成及干扰精子发生[49]. 由细菌感染产生睾丸炎, 通常可用抗生素治疗, 如果不及时治疗, 会导致男性不育[50].

多种病毒感染可引起睾丸炎, 并严重损伤精子发生[42]. 腮腺炎病毒(mumps virus, MuV)经常诱导睾丸炎[51], 在未成年人中, MuV诱导的睾丸炎通常可以恢复, 但在成年人中MuV感染可导致不育[52]. 人类免疫缺陷病毒(human immunodeficiency virus, HIV)感染也常引起睾丸炎, 并损伤睾丸功能[53]. 此外, 柯萨奇病毒(coxsackie virus)、流感病毒(influenza virus)以及登革热病毒(dengue virus, DENV)与睾丸炎有关[54]. 值得注意的是, 这些引起睾丸炎的病毒都是RNA病毒, 而DNA病毒感染很少引起睾丸炎, 其中的机理是值得关注的重要问题.

T. gondii 是分布全球的寄生虫, 感染人后可损害睾丸功能, 并与男性不育有关[55]. *T. gondii* 感染啮齿动物后, 会入侵睾丸, 并促进生殖细胞凋亡[56], 但尚无证据表明*T. gondii*感染人类睾丸. 由于微生物可以激活睾丸细胞的PRR, 启动固有免疫应答. 因此, 睾丸细胞可能参与启动睾丸炎的产生, 这一问题有待澄清.

4 结语

虽然睾丸具有免疫豁免环境和固有防御系统, 一些病理因素可破坏睾丸免疫稳态, 损害男性生育能力. 深入研究睾丸免疫调节机制对防治相关疾病

具有重要意义，以下问题可作为将来研究的重点：(ⅰ) 近来发现TAM受体在维持睾丸豁免中行使重要功能，特别是TAM受体可以调节对生精细胞抗原的免疫耐受，TAM受体调节睾丸免疫平衡的机制值得深入研究. (ⅱ) 主要睾丸细胞广泛表达PRR，并启动固有免疫应答，PRR在睾丸细胞抵御微生物感染中的功能需要进一步验证. (ⅲ) PRR启动的睾丸细胞固有免疫应答产生大量炎症因子，这些细胞因子对睾丸功能的影响有待澄清. (ⅳ) 一些证据表明，生精细胞可以抵御微生物感染. 生精细胞的防御能力值得特别关注，因为这类细胞占睾丸细胞的绝大多数. 特别是BTB内侧的管腔，与间质中的免疫成分隔离，生精细胞的天然防御能力可能在抵御来自下游生殖管道的病原体中至关重要. 对以上问题的深入研究将进一步揭示睾丸免疫调节机制及其对男性生育的影响，这不仅有助于防治免疫相关的睾丸功能损伤与男性不育，而且可能为抑制器官移植中的免疫排斥及诱导组织特异的抗感染能力提供线索.

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Summary for “睾丸免疫调节与睾丸炎: Tyro3/Axl/Mer 受体酪氨酸激酶与模式识别受体的功能”

Testicular immunomodulation and orchitis: Roles of Tyro3/Axl/Mer receptor tyrosine kinases and pattern recognition receptors

JIANG Qian, ZHAO Xiang, XUE ShePu & HAN DaiShu*

Department of Cell Biology, Institute of Basic Medical Science, Chinese Academy of Medical Sciences; School of Basic Medicine, Peking Union Medical College, Beijing 100005, China
* Corresponding author, E-mail: dshan@ibms.pumc.edu.cn

Human infertility affects approximately 15% of couples at reproductive age worldwide. Male factors contribute up to 45% of infertility cases. Inflammatory conditions in the male genital system are responsible for about 10% of male infertility in developed countries, and the incidence of immunological infertility can be considerably higher in developing countries where medical cares and environment conditions are poor. In particular, immunological disorders in the testis freguently cause infertility because it is a organ where spermatogenesis carries out.

The testis possesses a special immune environment because of its immunoprivileged status and innate immune system. Testicular immune privilege is essential for the protection of male germ cells from detrimental immune responses, whereas the local innate immune system plays a crucial role in the testicular defense against microbial infections. Most of testicular cells are involved in the regulation of testicular immune homeostasis. Disruption of testicular immune homeostasis may result in orchitis, one aetiological factor of male infertility. Multiple mechanisms cooperatively regulate testicular immune homeostasis. Recent studies have revealed important roles of Tyro3/Axl/Mer (TAM) receptor tyrosine kinases and pattern recognition receptors (PRRs) in regulating testicular immune environment.

TAM receptors belong to one subfamily of receptor tyrosine kinases. The product of growth arrest-specific gene 6 (Gas6) is common ligand of TAM receptors. TAM and Gas6 are expressed in the testis. TAM triple knockout mice are male sterile and develop autoimmune orchitis. TAM receptors regulate testicular immune homeostasis via three mechanisms: (i) PRR-initiated innate immune responses in Sertoli and Leydig cells are inhibited by TAM/Gas6 signaling, which reduce inflammatory cytokine production in the testis; (ii) TAM receptors promote phagocytosis of apoptotic germ cells by Sertoli cells. The phagocytic clearance of apoptotic germ cells by Sertoli cells can remove germ cell antigens, thereby preventing endogenous immune response; (iii) TAM receptors favor systemic immune tolerance to male germ cells. Experimental autoimmune orchitis (EAO) is a testis-specific autoimmune inflammation in rodent animals after immunization with male germ cell antigens. Axl and Mer double knockout mice are susceptible to EAO induction, suggesting Axl and Mer cooperatively regulate the systemic immune tolerance to male germ cell antigens.

Although the testis is an immunoprivileged organ, it can be infected by a broad spectrum of microbial pathogens. However, the testis usually recovers from microbial infections without evident inflammatory response, suggesting that the testis adopts an effective local innate defense system against invading microorganisms. Recognition of microbial pathogens by PRRs initiates innate immune responses, which is the first line of the host defense against invading microbes. Several subfamilies of PRRs are expressed in the testis. In particularly, major testicular cells, including Sertoli, Leydig, and male germ cells, express various PRRs. PRRs can be activated in testicular cells by pathogen molecular patterns, thereby initiating innate immune responses. These observations indicate that testicular cells are equipped with innate immune machinery and may be involved in the testicular defense against microbial infections. This article describes role of TAM receptors and PRRs in regulating immune environment in the testis, and speculates aspects of which need priorizing in future investigation.

testicular immunity, Tyro3/Axl/Mer receptor, pattern recognition receptor, orchitis, male infertility

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