[Frontiers in Bioscience, Landmark, 21, 316-327, January 1, 2016]

The roles of TAM receptor tyrosine kinases in the mammalian testis and immunoprivileged sites

Tingting Deng[1], Qiaoyuan Chen[2], Daishu Han[2]

[1]Institute of Clinical Medical Sciences, China-Japan Friendship Hospital, Beijing, China, [2]Department of Cell Biology, Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences, School of Basic Medicine, Peking Union Medical College, Beijing, China

TABLE OF CONTENTS

1. ABSTRACT

Three members of a receptor tyrosine kinase family, including Tyro3, Axl, and Mer, are collectively called as TAM receptors. TAM receptors have two common ligands, namely, growth arrest specific gene 6 (Gas6) and protein S (ProS). The TAM-Gas6/ProS system is essential for phagocytic removal of apoptotic cells, and plays critical roles in regulating immune response. Genetic studies have shown that TAM receptors are essential regulators of the tissue homeostasis in immunoprivileged sites, including the testis, retina and brain. The mechanisms by which the TAM-Gas6/ProS system regulates the tissue homeostasis in immunoprivileged sites are emerging. The roles of the TAM-Gas6/ProS system in regulating the immune privilege were intensively investigated in the mouse testis, and several studies were performed in the eye and brain. This review summarizes our current understanding of TAM signaling in the testis and other immunoprivileged tissues, as well as highlights topics that are worthy of further investigation.

2. INTRODUCTION

Immunoprivileged tissues are body sites with special immune microenvironments wherein the systemic immune responses to allo- and auto-antigens are significantly reduced (1). Remarkable immunoprivileged tissues in mammals include the testis, eye, brain, and pregnant uterus (2). The immunoprivileged status in these tissues is essential to fulfill their indispensable functions for the maintenance of the species. Although the microenvironments in these tissues exhibit different self-preserving functions, the common goal of the immune privilege is to protect the tissues from detrimental immune response.

Both local immunosuppressive milieu and systemic immune tolerance are involved in the regulation of the immune privilege (3). However, mechanisms underlying immune privilege are not the same among individual immunoprivileged sites because of the difference in physical structures and cellular contents of the tissues. The testis consists of various cells constituting two compartments, namely, the seminiferous tubules and the interstitial spaces (Figure 1). Male germ cells are differentiated in the seminiferous epithelium that is built from Sertoli cells intimately embracing the male germ cells. The blood–testis barrier (BTB), which is formed between two adjacent Sertoli cells by several junction types, separates the germ cell antigens in the tubular lumen from the immunological components in the

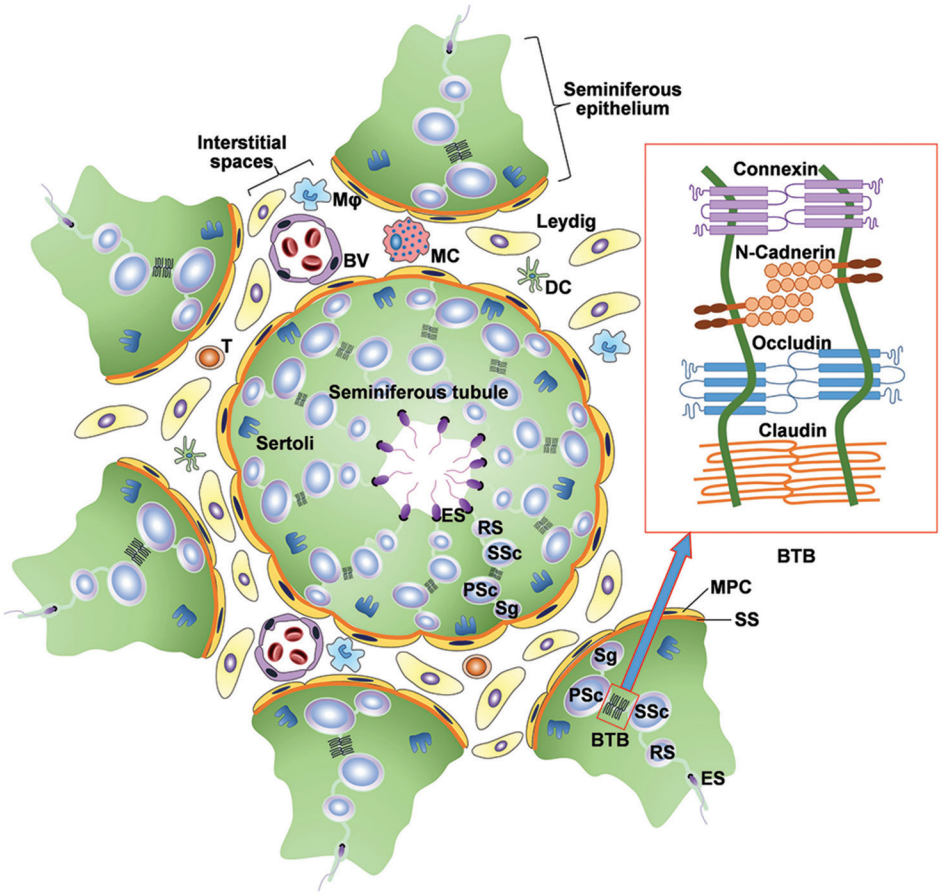

Figure 1. Schematic of the mammalian testis. The testis consists of two compartments: seminiferous tubule and interstitial space. The seminiferous tubule is surrounded by myoid peritubular cells (MPCs). MPCs, together with secretion substances (SS) that are produced by Sertoli cells, form the tubular basal lamina to enclose the seminiferous epithelium. The seminiferous epithelium is built by columnar Sertoli cells that embrace different stages of developing germ cells, including spermatogonia (Sg), primary spermatocytes (PSc), secondary spermatocytes (SSc), round spermatids (RS), and elongating spermatids (ES). The blood-testis barrier (BTB) is formed by different junctions between two adjacent Sertoli cells. The interstitial spaces contain mainly Leydig cells and minor immune cells, including macrophages (Mϕ), T lymphocytes, dendritic cells (DCs), and mast cells (MC). Blood vessels (BV) are located in the interstitial spaces.

interstitial spaces. Testosterone is synthesized by Leydig cells in the interstitial spaces. The interstitial spaces also contain blood, lymphatic vessels, and various immune cells, which are mainly macrophages, minor T lymphocytes, mast cells, and dendritic cells (DCs). The seminiferous tubules and the interstitial spaces exhibit immunoprivileged properties (4). Several reviews are consulted for the underlying mechanisms of the testicular immune privilege (3,5-7). Increasing evidence shows that Tyro3, Axl, and Mer (TAM) receptor tyrosine kinases, as well as their two ligands growth arrest specific gene 6 (Gas6) and protein S (ProS), cooperatively regulate the immunoprivileged status in the testis, eye, and brain.

TAM receptor belongs to an unique receptor tyrosine kinase family (8). Tyro3, Axl, and Mer share a similar structure containing two immunoglobulin (Ig)-like domains and two fibronectin type β (FN β) repeats in their extracellular regions, followed by a transmembrane domain and an intracellular protein tyrosine kinase domain (Figure 2). Their two ligands Gas6 and ProS are also identified (9,10). Gas6 and ProS contain an N-terminal gamma-carboxylated glutamic acid (GLA) followed by four epidermal growth factor (EGF)-like domains and a C-terminal sex hormone binding globulin (SHBG)-like domain (Figure 2). Two Ig-like domains in the extracellular N-terminal of TAM receptors bind SHBG-like domains of Gas6 or ProS, which activate intracellular tyrosine kinase and initiate cytoplasmic signaling pathway to regulate multiple biological processes, including survival and proliferation of cells, regulation of innate immunity, and phagocytosis of apoptotic cells. The generation of TAM receptors and their ligand knockout mice promoted the understanding of this system (11-13). Increasing evidence states that TAM signaling negatively regulates the innate immune response and plays a critical role in the resolution of inflammation (14,15). Moreover, TAM receptors facilitate

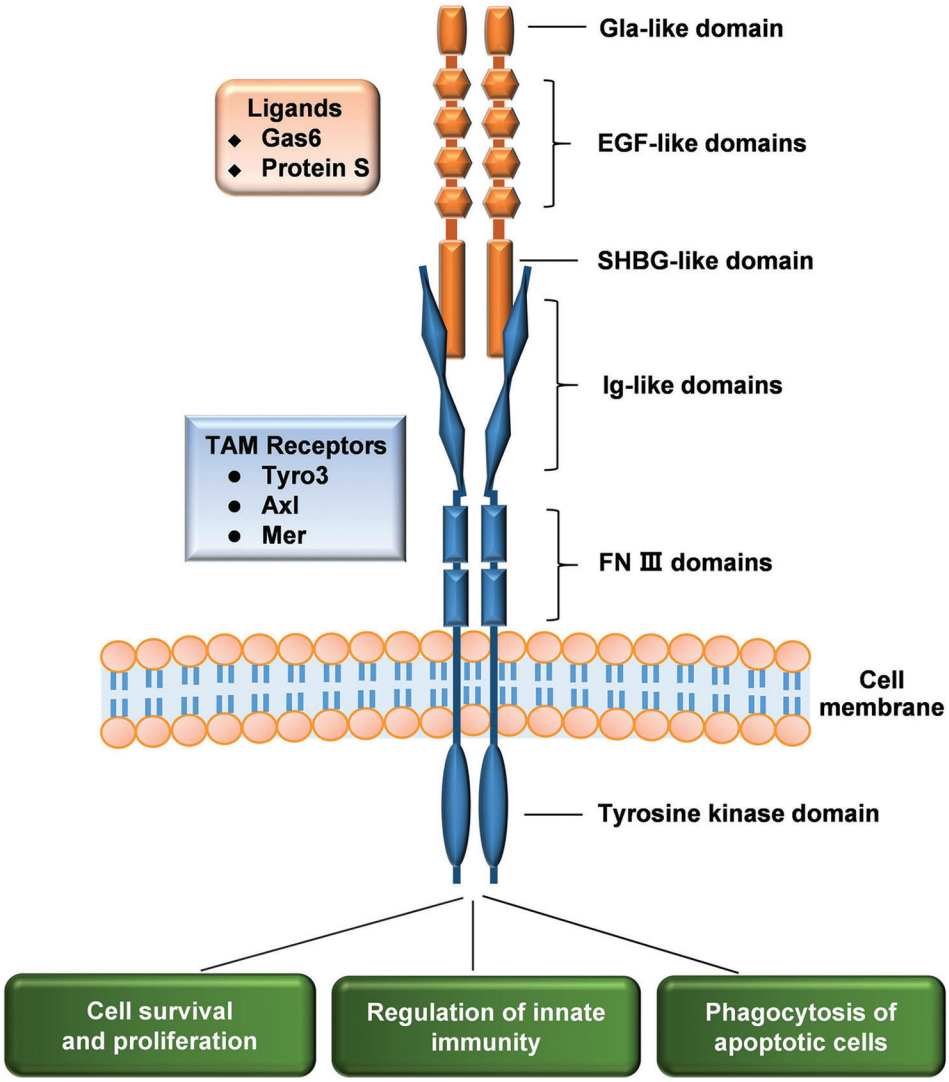

Figure 2. Schematic of TAM receptors and their ligands. TAM receptors contain three members: Tyro3, Axl, and Mer. These members share a similar structure containing two Ig-like domains at N-terminal followed by two extracellular FN β domains, a transmembrane domain and an intracellular protein tyrosine kinase domain at C-terminal. Gas6 and protein S are two ligands of TAM receptors. The two ligands share a common structure composed of an N-terminal Gla domain, four EGF domains and a C-terminal SHBG domain. Recognition of TAM receptors by ligands initiates intracellular signaling to regulate various biological pathways, including cell survival and proliferation, regulation of innate immune response, and uptake of apoptotic cells. Gla, Gamma-carboxylated glutamic acid; EGF, epidermal growth factor; SHBG, hormone binding globulin; FN β, fibronectin type β; Gas6, growth arrest specific gene 6.

phagocytic removal of apoptotic cells, thereby preventing autoimmune diseases (16-20).

The most evident tissue-specific phenotypes in TAM triple knockout ($TAM^{-/-}$) mice include male sterility caused by impaired spermatogenesis, blindness caused by degeneration of photoreceptors in the retina, and damages in the brain (13), suggesting that TAM receptors help maintain the tissue homeostasis of immunoprivileged sites. Although the roles of TAM receptors in regulating systemic immune homeostasis were recently reviewed, their tissue-specific functions in immunoprivileged sites are yet to be consulted. This article discusses the current understanding about TAM receptors in the testis and other immunoprivileged tissues.

3. TAM RECEPTORS IN THE TESTIS

3.1. TAM and Gas6 expression in the testis and male infertility of $TAM^{-/-}$ mice

Male $TAM^{-/-}$ mice are sterile because of the progressive loss of spermatogenesis, indicating that TAM receptors play essential roles in the maintenance of testicular function (13). To reveal the roles of TAM receptors in the testis, we examined the expression of TAM and Gas6 in the development of a postnatal

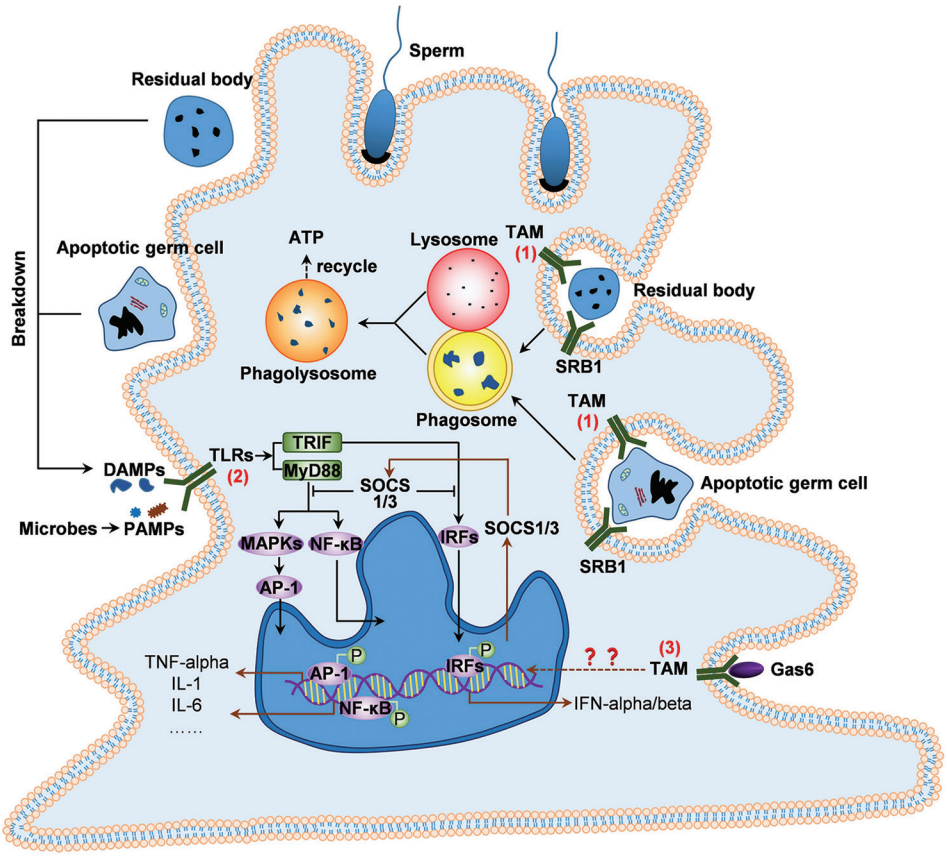

Figure 3. Functions of TAM receptors and TLRs in Sertoli cell. (1) TAM-mediated phagocytosis of apoptotic germ cells and residual bodies by Sertoli cells. After the phagocytosis, phagosome containing apoptotic cells or residual bodies fuses with lysosome to form phagolysosome. The apoptotic cells and residual bodies are degraded by enzymes of lysosome, and are recycled to produce energy for Sertoli cells. (2) TLR-initiated innate immune response. Residual bodies and apoptotic germ cells that are not timely removed by Sertoli cells break down and release damage-associated molecular patterns (DAMPs) which can activate TLRs on Sertoli cell surface. TLRs can also be activated by pathogen-associated molecular pattern (PAMPs) of microbes. TLR activation initiates TRIF- and MyD88-dependent pathways, thereby inducing pro-inflammatory cytokines (TNF-alpha, IL-1, IL-6) and type 1 interferon (IFN-alpha/beta) through the activation of transcription factors AP-1, NF-κB, and IRFs. (3) Negative regulation of TLR pathways by TAM signaling. After recognition of Gas6, TAM receptors initiate undefined signaling to induce SOCS1/3 expression. SOCS1/3 inhibits the activation of the transcription factors, thus reducing TLR-initiated innate immune response. AP-1, activator protein 1; NF-κB, nuclear factor κB; IRFs, IFN regulatory factors; SOCS, suppressor of cytokine signaling proteins.

mouse testis (21). All three TAM receptors are abundantly expressed in Sertoli cells, but Axl and Mer are also expressed in Leydig cells. By contrast, Gas6 is exclusively expressed in Leydig cells. Notably, germ cells do not express TAM receptors and Gas6.

The impaired spermatogenesis in TAM$^{-/-}$ mice evidently appeared about five weeks, after birth, following the onset of sexual maturation and sperm production (22). Although TAM$^{-/-}$ mice are sterile males, they can fulfill the first wave of spermatogenesis and produce minor sperm with multiple morphological malformations. As the mice aged, the germ cells are progressively lost starting from elongated spermatids to round spermatids, spermatocytes, spermatogonia, and eventually depleted from the seminiferous tubules. The defective spermatogenesis cannot be cell autonomous because the germ cells do not express TAM receptors. Testosterone synthesis in Leydig cells is not affected in TAM$^{-/-}$ mice, suggesting that the defective spermatogenesis is attributed to the potential impairment of Sertoli cell functions (22).

3.2. Involvement of TAM and Gas6 in the uptake of apoptotic germ cells by Sertoli cells

Sertoli cells are only somatic cells within the seminiferous tubules which create an essential microenvironment for spermatogenesis. Sertoli cells provide tropic support to germ cells and phagocytically remove apoptotic germ cells and residual bodies (Figure 3, right). The phagocytic removal of apoptotic germ cells and residual bodies by Sertoli cells is necessary for intrinsic homeostasis and normal spermatogenesis (23). We demonstrated that the TAM-Gas6 system is essential for phagocytic removal of apoptotic germ cells by Sertoli cells (24). TAM receptors collaboratively mediate the

phagocytosis of apoptotic germ cells by Sertoli cells. Mer is responsible for triggering phagocytic signaling, whereas Axl and Tyro3 contribute to the recognition and tethering of apoptotic germ cells by Sertoli cells (24). About 75% of spermatogenic cells undergo apoptosis under physiological conditions (25). Additionally, the most cytoplasmic portions of elongated spermatids are shed as residual bodies before sperm cells are released into the lumen of the seminiferous tubules (26). The phagocytic removal of apoptotic cells indicates more than mere waste disposal. Moreover, apoptotic germ cells and residual bodies can become energy sources for Sertoli cells to produce ATP (27) (Figure 3). The phagocytic removal of apoptotic cells prevents autoimmune response by eliminating endogenous autoantigens (28). The impaired phagocytic removal of apoptotic cells is associated with systemic autoimmune diseases (29,30). Mature sperms are exclusively produced within the post-pubertal period, a long time after immunocompetence is established during fetal and early neonatal life. Therefore, several immunogenetic autoantigens are produced by developing germ cells (31). TAM-mediated phagocytic removal of apoptotic germ cells by Sertoli cells will contribute to the maintenance of immunoprivileged status in the testis because the defective removal of apoptotic germ cells induces endogenous inflammation in the testis and may lead to autoimmune orthitis (32).

3.3. Induction of endogenous inflammation by damaged germ cells

Toll-like receptors (TLRs) initiate innate immune response and direct antigen-specific adaptive immunity after recognition of conserved microbial molecular patterns. (33,34). TLRs can also recognize endogenous ligands that can be released from damaged cells, thereby inducing autoimmune response (35). Among the most characterized endogenous ligands, high-mobility group box 1 (HMGB1) and several heat shock proteins (HSPs) trigger endogenous inflammation through the activation of TLR2 and TLR4 (36,37). HMGB1 and HSPs are abundantly expressed in male germ cells (38, 39). Testicular HSPs are involved in the development of infectious and autoimmune orchitis (40,41). We demonstrated that damaged male germ cells induce inflammatory cytokine expression in Sertoli cells through TLRs (Figure 3, left) (42). A previous study confirmed the involvement of HMGB1 in the onset of autoimmune orchitis (43). Accordingly, we clarified that TLR2 and TLR4 mediate experimental autoimmune orchitis (EAO) induction in mice. These observations suggested that TLR-initiated immune response to testicular autoantigens is associated with autoimmune orchitis.

3.4. Inhibition of TLR-initiated testicular innate immune response

TAM receptors are pleiotropic inhibitors of TLR-initiated systemic innate immune response (14). The mechanisms by which TAM receptors regulate immune homeostasis were further investigated (44,45), and these studies proved that TAM signaling inhibits inflammation by limiting the intensity and duration of innate immune response. The abundant expression of TAM receptors and Gas6 in the testis suggests that they inhibit immune response in this organ, thereby contributing to the maintenance of the testicular immune privilege. In fact, TAM-Gas6 signaling inhibits TLR-initiated inflammatory response in Sertoli and Leydig cells (46,47). We further found that the testicular immune privilege in $TAM^{-/-}$ mice is progressively disrupted after sexual maturation (48). $TAM^{-/-}$ male mice spontaneously develop autoimmune orchitis, which is characterized by macrophage and lymphocyte infiltrations into the testis, breakdown of BTB, and generation of autoantibodies against germ cell antigens. Moreover, inflammatory cytokines, including TNF-alpha, IL-6 and MCP-1, are upregulated in the $TAM^{-/-}$ testis. The cytokine upregulation is evident in Sertoli cells, suggesting that the innate immune response is induced in Sertoli cells because of deficient TAM receptors (48). This observation corresponds to our previous finding that TAM-Gas6 system inhibits TLR-mediated inflammatory cytokine expression in Sertoli cells (46). Autoimmune orchitis in $TAM^{-/-}$ mice is exclusively developed after the onset of sexual maturation, at which a large number of germ cells underwent apoptosis and numerous residual bodies were formed. Considering that the phagocytic ability of $TAM^{-/-}$ Sertoli cells is impaired and damaged germ cells induce inflammatory response in Sertoli cells through TLR activation (24,42), we speculate that the TAM-Gas6 system is essential in maintaining the immunoprivileged status in the testis through the promotion of phagocytic removal of apoptotic germ cells and residual bodies by Sertoli cells, as well as the inhibition of TLR-initiated innate immune response in the testicular cells (Figure 3).

3.5. Roles of TAM receptors in tolerating germ cell antigens

In addition to local immunosuppression, the systemic immune tolerance to autoantigens also contributes to the immunoprivileged status. TAM receptors regulate the systemic immune tolerance to germ cell autoantigens. Compared with $TAM^{-/-}$ male mice, which are sterile and eventually developing autoimmune orchitis, Axl and Mer double knockout ($Axl^{-/-}Mer^{-/-}$) male mice demonstrate normal fertility (22,48). However, $Axl^{-/-}Mer^{-/-}$ mice are susceptible to EAO induction, suggesting that Axl and Mer are important regulators of the systemic immune tolerance to male germ cell antigens (49). EAO is a rodent model for investigating the mechanisms underlying the pathogenesis of autoimmune orchitis, which can be induced by immunizing rodent animals with allogeneic testicular antigens (50). $Axl^{-/-}Mer^{-/-}$ mice develop severe EAO after a single immunization with germ cell antigens emulsified with complete Freund's adjuvant, which is characterized by infiltration of circulating macrophages and T lymphocytes into the testis, damage

of the seminiferous epithelium, impaired permeability of BTB, and generation of autoantibodies against germ cell antigens (50). By contrast, a single immunization does not induce EAO in wild-type (WT) mice. However, mild EAO is developed in $Axl^{-/-}$ or $Mer^{-/-}$ mice after the same immunization, whereas $Tyro3^{-/-}$ mice are not susceptible to EAO induction (49). These observations suggest that Axl and Mer, but not Tyro3, cooperatively regulate the systemic immune tolerance to male germ cell antigens, which is in agreement with the observation that Axl and Mer, but not Tyro3, are expressed in antigen-presenting cells, including dendritic cells and macrophages (14). The mechanisms by which Axl and Mer regulate immune response to germ cell autoantigens represent an important topic for future investigation.

3.6. Roles of TLRs in mediating immune response to germ cell antigens

Autoimmune orchitis is an etiological factor of male infertility (51). The mechanisms that mediate systemic autoimmune response to germ cell antigens are largely unknown. Considering that TAM receptors are inhibitors of TLR-initiated innate immune response and TLRs may initiate autoimmune response to endogenous ligands (52), we speculate that TLRs will mediate autoimmune response to male cell antigens. This hypothesis was proven by our recent study showing that TLR2 and TLR4 cooperatively mediate EAO induction in mice (53). WT mice developed severe autoimmune orchitis after three immunizations with autoantigens. TLR2 or TLR4 knockout mice exhibited relatively low susceptibility to EAO induction compared with WT mice. Remarkably, TLR2 and TLR4 double-knockout mice are almost completely protected from EAO induction. Therefore, Axl/Mer receptors and TLR2/4 regulate systemic autoimmune response to germ cell antigens in opposite manners.

4. TAM RECEPTORS IN THE EYE

4.1. Mer receptor is essential for vision

When $TAM^{-/-}$ mice were initially generated, they were recognized as blind because of photoreceptor degeneration (13). The role of TAM receptors in maintaining the retinal homeostasis was confirmed by finding that Mer mutation is responsible for the inherited photoreceptor degeneration in a rat model of retinitis pigmentosa (54). Photoreceptor degeneration can also be observed in Mer single-knockout mice, confirming that Mer plays a critical role in regulating retinal function (55). In agreement with these observations, Mer mutation accounts for a subset of inherited retinitis pigmentosa in humans (56,57).

4.2. Role of Mer in regulating phagocytosis of photoreceptor segments

The mechanisms by which Mer regulates the retinal homeostasis were investigated. The photoreceptor degeneration caused by Mer mutation is cell non-autonomous and reflects the impaired function of the retinal pigment epithelium (RPE) cells (58), which form a highly organized epithelium at the back of the eye. These cells phagocytose the distal ends of outer photoreceptor segments, which are critical in maintaining a constant outer segment length and tissue homeostasis because a large number of outer segment membranes are produced daily. Thus, RPE cell dysfunction may result in various retinal diseases (59). RPE cells in $Mer^{-/-}$ mice exhibit a defect in phagocytically removing photoreceptor components, thereby leading to RPE degeneration and blindness as mice aged (58). RPE cells express Mer and Tyro3, and loss of Mer function downregulates Tyro3 expression in RPE cells (58), suggesting that Mer and Tyro3 cooperatively regulate RPE cell function.

4.3. Immune privilege in the eye

The eye is a remarkable immunoprivileged site (60). In fact, substantial knowledge about immune privilege resulted from investigations on the eye (61). However, non-infectious uveitis commonly threatens sight and is presumed to be an autoimmune disease (62,63). Experimental autoimmune uveitis (EAU) can be induced by immunization of susceptible animals with a purified autoantigen, interphotoreceptor retinoid-binding protein (IRBP) (64). Several TLRs mediate EAU induction, suggesting that TLR signaling is involved in the onset of autoimmune uveitis (65). By contrast, TAM receptors inhibit EAU induction. Immunization of $TAM^{-/-}$ mice with a low dose of IRBP induces the onset of EAU (66), but the same immunization does not induce EAU in WT mice. Further research shows that IRBP immunization predominantly induces Th1 effector response in $Axl^{-/-}$ $Mer^{-/-}$ mice (67). The effect will be cell non-autonomous because T cells do not express Axl and Mer. However, DCs and macrophages express Axl and Mer (14). DCs and macrophages of $Axl^{-/-}Mer^{-/-}$ mice drive Th1 cell differentiation by producing high levels of IL-12 and IL-18.

5. TAM RECEPTORS IN THE BRAIN

The brain was thought to be an immunoprivileged tissue because of the blood–brain barrier (BBB) (68). Although all three TAM receptors are expressed in the brain (69), their roles in this tissue are less understood compared with their roles in the testis and the eye; however, TAM signaling in the regulation of immunoprivileged status in the brain was recently revealed. Tyro3-ProS signaling prevents the disruption of BBB by oxygen/glucose deprivation (70). Inflammatory brain damage and BBB disruption are observed in $TAM^{-/-}$ mice, and antibody deposition and autoreactive T cell infiltration occur in the brain (71). A recent study showed that TAM receptors favor brain neurogenesis by inhibiting microglial cell activation (72). Microglial cells of $TAM^{-/-}$ mice produce high levels of pro-inflammatory cytokines, including IL-6, IL-1beta and TNF-alpha, in

response to lipopolysaccharide (LPS) challenge. LPS is a TLR4 agonist that triggers inflammatory response through TLR4 signaling. Several TLRs are expressed in microglial cells and can be activated by their respective ligands (73). TAM receptors can inhibit microglial cell activation through the negative regulation of TLR signaling, thereby restricting intensity and duration of inflammatory response in microglial cells to TLR ligands.

6. TAM FUNCTION BEYOND THE IMMUNOPRIVILEGED TISSUES

The liver demonstrates special immunoregulatory mechanisms. Although the liver is constantly exposed to microbial products derived from enteric microflora under physiological conditions, no obvious inflammation occurs, which represents a behavior termed as "liver tolerance" (74). However, autoimmune hepatitis (AIH) is a global disease in diverse ethnic groups (75). An evidence shows that TAM receptors participate in maintaining the liver tolerance (76). TAM$^{-/-}$ mice develop persistent inflammatory liver damage resembling AIH, which is manifested by the appearance of interface hepatitis, immune cell infiltrations and elevated inflammatory cytokine levels in the liver. TAM receptors, Gas6 and ProS are abundantly expressed in different cell types of the liver. Tyro3 is only expressed in Kupffer cells, Axl is ubiquitously expressed in all liver cells, and Mer is predominantly expressed in Kupffer and sinusoidal cells. By contrast, Gas6 and ProS are exclusively expressed in liver parenchymal cells. The liver of TAM$^{-/-}$ mice produces high levels of pro-inflammatory cytokines. Various TLRs are expressed in the liver, and overactivation of TLRs may break the liver tolerance and result in AIH (77). TAM receptors can inhibit TLR signaling in hepatic cells under physiological conditions, which remain to be clarified.

TAM receptors and their ligands exhibit multiple other functions, including regulation of platelet stabilization, hemostasis and vascular permeability (11,12,78). TAM receptors are also required for normal megakaryocytopoiesis and platelet production, which are involved in hemostasis regulation (79). Moreover, TAM receptors regulate erythropoiesis (80). The roles of TAM receptors in carcinogenesis are emerging (81). Increasing evidence shows that TAM receptors mediate viral entry (82-85). DCs may be susceptible to viral infection through the inhibition of innate antiviral responses by TAM signaling (86). These recent progresses indicate that TAM receptors play broad roles in many biological processes, which are worthy of further investigation.

7. CONCLUDING REMARKS

The TAM-Gas6/ProS system plays important roles in regulating numerous biological processes. The key functions of the TAM-Gas6/ProS system include the TAM-mediated phagocytic removal of apoptotic cells and the inhibition of innate immune response, given that sustained endogenous inflammation can lead to a broad spectrum of autoimmune diseases, which are the most evident phenotypes in TAM$^{-/-}$ mice. Cross-talk among TAM functions is important to converge their broad roles, which is worthy of future investigation. In addition to systemic immune disorders, the most severe tissue-specific defects appear in the immunoprivileged sites in TAM$^{-/-}$ mice, including the testis, eye, and brain. Therefore, the roles of TAM receptors in regulating the immune privilege merit further investigation. In this context, Tyro3 deserves great attention. Although Tyro3 is not expressed in immune cells, it is abundantly expressed in all immunoprivileged tissues. In particular, evident defective tissue homeostasis was observed in the immunoprivileged tissues of TAM$^{-/-}$ mice, suggesting that Tyro3 functions in these tissues. Further investigation on the functions of TAM receptors in the immunoprivileged tissues will provide novel insights into the mechanisms underlying autoimmune diseases.

8. ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (Grant Nos: 31171445, 31261160491, 31371518 and 81400421) and Major State Basic Research Project of China (No. 2015CB94300).

9. REFERENCES

1. E. Simpson: A historical perspective on immunological privilege. *Immunol Rev* 213, 12-22 (2006)
DOI: 10.1111/j.1600-065X.2006.00434.x
2. J. Stein-Streilein and R. R. Caspi: Immune privilege and the philosophy of immunology. *Front Immunol* 5, 110 (2014)
DOI: 10.3389/fimmu.2014.00110
3. N. Li, T. Wang and D. Han: Structural, cellular and molecular aspects of immune privilege in the testis. *Front Immunol* 3, 152 (2012)
DOI: 10.3389/fimmu.2012.00152
4. M. Fijak, S. Bhushan and A. Meinhardt: Immunoprivileged sites: the testis. *Methods Mol Biol* 677, 459-70 (2011)
DOI: 10.1007/978-1-60761-869-0_29
5. G. Kaur, P. Mital and J. M. Dufour: Testisimmune privilege - Assumptions facts. *Anim Reprod* 10(1), 3-15 (2013)
(doi not found)
6. S. Zhao, W. Zhu, S. Xue and D. Han: Testicular defense systems: immune privilege and innate immunity. *Cell Mol Immunol* 11(5), 428-37 (2014)
DOI: 10.1038/cmi.2014.38

7. H. MP: Immune Privilege of the Testis: Meaning, Mechanisms,and Manifestations. In: Springer, New York (2012)
(doi not found)

8. C. Lai and G. Lemke: An extended family of protein-tyrosine kinase genes differentially expressed in the vertebrate nervous system. *Neuron* 6(5), 691-704 (1991)
DOI: 10.1016/0896-6273(91)90167-X

9. T. N. Stitt, G. Conn, M. Gore, C. Lai, J. Bruno, C. Radziejewski, K. Mattsson, J. Fisher, D. R. Gies, P. F. Jones, P. Masiakowski, T. E. Ryan, N. J. Tobkes, D. H. Chen, P. S. DiStefano, G. L. Long, C. Basilico, M. P. Goldfarb, G. Lemke, D. J. Glass and G. D. Yancopoulos: The anticoagulation factor protein S and its relative, Gas6, are ligands for the Tyro 3/Axl family of receptor tyrosine kinases. *Cell* 80(4), 661-70 (1995)
DOI: 10.1016/0092-8674(95)90520-0

10. P. J. Godowski, M. R. Mark, J. Chen, M. D. Sadick, H. Raab and R. G. Hammonds: Reevaluation of the roles of protein S and Gas6 as ligands for the receptor tyrosine kinase Rse/Tyro 3. *Cell* 82(3), 355-8 (1995)
DOI: 10.1016/0092-8674(95)90424-7

11. T. Burstyn-Cohen, M. J. Heeb and G. Lemke: Lack of protein S in mice causes embryonic lethal coagulopathy and vascular dysgenesis. *J Clin Invest* 119(10), 2942-53 (2009)
DOI: 10.1172/JCI39325

12. A. Angelillo-Scherrer, P. de Frutos, C. Aparicio, E. Melis, P. Savi, F. Lupu, J. Arnout, M. Dewerchin, M. Hoylaerts, J. Herbert, D. Collen, B. Dahlback and P. Carmeliet: Deficiency or inhibition of Gas6 causes platelet dysfunction and protects mice against thrombosis. *Nat Med* 7(2), 215-21 (2001)
DOI: 10.1038/84667

13. Q. Lu, M. Gore, Q. Zhang, T. Camenisch, S. Boast, F. Casagranda, C. Lai, M. K. Skinner, R. Klein, G. K. Matsushima, H. S. Earp, S. P. Goff and G. Lemke: Tyro-3 family receptors are essential regulators of mammalian spermatogenesis. *Nature* 398(6729), 723-8 (1999)
DOI: 10.1038/19554

14. C. V. Rothlin, S. Ghosh, E. I. Zuniga, M. B. Oldstone and G. Lemke: TAM receptors are pleiotropic inhibitors of the innate immune response. *Cell* 131(6), 1124-36 (2007)
DOI: 10.1016/j.cell.2007.10.034

15. G. Lemke and C. V. Rothlin: Immunobiology of the TAM receptors. *Nat Rev Immunol* 8(5), 327-36 (2008)
DOI: 10.1038/nri2303

16. Q. Lu and G. Lemke: Homeostatic regulation of the immune system by receptor tyrosine kinases of the Tyro 3 family. *Science* 293(5528), 306-11 (2001)
DOI: 10.1126/science.1061663

17. G. Lemke and T. Burstyn-Cohen: TAM receptors and the clearance of apoptotic cells. *Ann N Y Acad Sci* 1209, 23-9 (2010)
DOI: 10.1111/j.1749-6632.2010.05744.x

18. J. H. van der Meer, T. van der Poll and C. van 't Veer: TAM receptors, Gas6, and protein S: roles in inflammation and hemostasis. *Blood* 123(16), 2460-9 (2014)
DOI: 10.1182/blood-2013-09-528752

19. C. V. Rothlin and G. Lemke: TAM receptor signaling and autoimmune disease. *Curr Opin Immunol* 22(6), 740-6 (2010)
DOI: 10.1016/j.coi.2010.10.001

20. G. Lemke: Biology of the TAM receptors. *Cold Spring Harb Perspect Biol* 5(11), a009076 (2013)
DOI: 10.1101/cshperspect.a009076

21. H. Wang, Y. Chen, Y. Ge, P. Ma, Q. Ma, J. Ma, S. Xue and D. Han: Immunoexpression of Tyro 3 family receptors--Tyro 3, Axl, and Mer--and their ligand Gas6 in postnatal developing mouse testis. *J Histochem Cytochem* 53(11), 1355-64 (2005)
DOI: 10.1369/jhc.5A6637.2005

22. Y. Chen, H. Wang, N. Qi, H. Wu, W. Xiong, J. Ma, Q. Lu and D. Han: Functions of TAM RTKs in regulating spermatogenesis and male fertility in mice. *Reproduction* 138(4), 655-66 (2009)
DOI: 10.1530/REP-09-0101

23. Y. Nakanishi and A. Shiratsuchi: Phagocytic removal of apoptotic spermatogenic cells by Sertoli cells: mechanisms and consequences. *Biol Pharm Bull* 27(1), 13-6 (2004)
DOI: 10.1248/bpb.27.13

24. W. Xiong, Y. Chen, H. Wang, H. Wu, Q. Lu and D. Han: Gas6 and the Tyro 3 receptor tyrosine kinase subfamily regulate the phagocytic function of Sertoli cells. *Reproduction* 135(1), 77-87 (2008)
DOI: 10.1530/REP-07-0287

25. L. Johnson, C. S. Petty and W. B. Neaves: Further quantification of human spermatogenesis: germ cell loss during postprophase of meiosis and its relationship to daily sperm production. *Biol Reprod* 29(1), 207-15 (1983)
DOI: 10.1095/biolreprod29.1.207

26. J. B. Kerr and D. M. de Kretser: Proceedings: The role of the Sertoli cell in phagocytosis of the residual bodies of spermatids. *J Reprod Fertil* 36(2), 439-40 (1974)
DOI: 10.1530/jrf.0.0360439

27. W. Xiong, H. Wang, H. Wu, Y. Chen and D. Han: Apoptotic spermatogenic cells can be energy sources for Sertoli cells. *Reproduction* 137(3), 469-79 (2009)
DOI: 10.1530/REP-08-0343

28. S. Nagata, R. Hanayama and K. Kawane: Autoimmunity and the clearance of dead cells. *Cell* 140(5), 619-30 (2010)
DOI: 10.1016/j.cell.2010.02.014

29. P. L. Cohen, R. Caricchio, V. Abraham, T. D. Camenisch, J. C. Jennette, R. A. Roubey, H. S. Earp, G. Matsushima and E. A. Reap: Delayed apoptotic cell clearance and lupus-like autoimmunity in mice lacking the c-mer membrane tyrosine kinase. *J Exp Med* 196(1), 135-40 (2002)
DOI: 10.1084/jem.20012094

30. R. Hanayama, M. Tanaka, K. Miyasaka, K. Aozasa, M. Koike, Y. Uchiyama and S. Nagata: Autoimmune disease and impaired uptake of apoptotic cells in MFG-E8-deficient mice. *Science* 304(5674), 1147-50 (2004)
DOI: 10.1126/science.1094359

31. P. Jacobo, V. A. Guazzone, M. S. Theas and L. Lustig: Testicular autoimmunity. *Autoimmun Rev* 10(4), 201-4 (2011)
DOI: 10.1016/j.autrev.2010.09.026

32. R. M. Pelletier, S. R. Yoon, C. D. Akpovi, E. Silvas and M. L. Vitale: Defects in the regulatory clearance mechanisms favor the breakdown of self-tolerance during spontaneous autoimmune orchitis. *Am J Physiol Regul Integr Comp Physiol* 296(3), R743-62 (2009)
DOI: 10.1152/ajpregu.90751.2008

33. A. Iwasaki and R. Medzhitov: Regulation of adaptive immunity by the innate immune system. *Science* 327(5963), 291-5 (2010)
DOI: 10.1126/science.1183021

34. T. Kawai and S. Akira: The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors. *Nat Immunol* 11(5), 373-84 (2010)
DOI: 10.1038/ni.1863

35. M. Li, Y. Zhou, G. Feng and S. B. Su: The critical role of Toll-like receptor signaling pathways in the induction and progression of autoimmune diseases. *Curr Mol Med* 9(3), 365-74 (2009)
DOI: 10.2174/156652409787847137

36. R. M. Vabulas, P. Ahmad-Nejad, C. da Costa, T. Miethke, C. J. Kirschning, H. Hacker and H. Wagner: Endocytosed HSP60s use toll-like receptor 2 (TLR2) and TLR4 to activate the toll/interleukin-1 receptor signaling pathway in innate immune cells. *J Biol Chem* 276(33), 31332-9 (2001)
DOI: 10.1074/jbc.M103217200

37. J. S. Park, D. Svetkauskaite, Q. He, J. Y. Kim, D. Strassheim, A. Ishizaka and E. Abraham: Involvement of toll-like receptors 2 and 4 in cellular activation by high mobility group box 1 protein. *J Biol Chem* 279(9), 7370-7 (2004)
DOI: 10.1074/jbc.M306793200

38. C. K. Zetterstrom, M. L. Strand and O. Soder: The high mobility group box chromosomal protein 1 is expressed in the human and rat testis where it may function as an antibacterial factor. *Hum Reprod* 21(11), 2801-9 (2006)
DOI: 10.1093/humrep/del256

39. M. Biggiogera, R. M. Tanguay, R. Marin, Y. Wu, T. E. Martin and S. Fakan: Localization of heat shock proteins in mouse male germ cells: an immunoelectron microscopical study. *Exp Cell Res* 229(1), 77-85 (1996)
DOI: 10.1006/excr.1996.0345

40. M. R. Metukuri, C. M. Reddy, P. R. Reddy and P. Reddanna: Bacterial LPS-mediated acute inflammation-induced spermatogenic failure in rats: role of stress response proteins and mitochondrial dysfunction. *Inflammation* 33(4), 235-43 (2010)
DOI: 10.1007/s10753-009-9177-4

41. M. Fijak, R. Iosub, E. Schneider, M. Linder, K. Respondek, J. Klug and A. Meinhardt: Identification of immunodominant autoantigens in rat autoimmune orchitis. *J Pathol* 207(2), 127-38 (2005)
DOI: 10.1002/path.1828

42. X. Zhang, T. Wang, T. Deng, W. Xiong, P.

Lui, N. Li, Y. Chen and D. Han: Damaged spermatogenic cells induce inflammatory gene expression in mouse Sertoli cells through the activation of Toll-like receptors 2 and 4. *Mol Cell Endocrinol* 365(2), 162-73 (2013) DOI: 10.1016/j.mce.2012.10.016

43. F. Aslani, H. C. Schuppe, V. A. Guazzone, S. Bhushan, E. Wahle, G. Lochnit, L. Lustig, A. Meinhardt and M. Fijak: Targeting high mobility group box protein 1 ameliorates testicular inflammation in experimental autoimmune orchitis. *Hum Reprod* 30(2), 417-31 (2015) DOI: 10.1093/humrep/deu320

44. E. A. Carrera Silva, P. Y. Chan, L. Joannas, A. E. Errasti, N. Gagliani, L. Bosurgi, M. Jabbour, A. Perry, F. Smith-Chakmakova, D. Mucida, H. Cheroutre, T. Burstyn-Cohen, J. A. Leighton, G. Lemke, S. Ghosh and C. V. Rothlin: T cell-derived protein S engages TAM receptor signaling in dendritic cells to control the magnitude of the immune response. *Immunity* 39(1), 160-70 (2013) DOI: 10.1016/j.immuni.2013.06.010

45. A. Zagorska, P. G. Traves, E. D. Lew, I. Dransfield and G. Lemke: Diversification of TAM receptor tyrosine kinase function. *Nat Immunol* 15(10), 920-8 (2014) DOI: 10.1038/ni.2986

46. B. Sun, N. Qi, T. Shang, H. Wu, T. Deng and D. Han: Sertoli cell-initiated testicular innate immune response through toll-like receptor-3 activation is negatively regulated by Tyro3, Axl, and mer receptors. *Endocrinology* 151(6), 2886-97 (2010) DOI: 10.1210/en.2009-1498

47. T. Shang, X. Zhang, T. Wang, B. Sun, T. Deng and D. Han: Toll-like receptor-initiated testicular innate immune responses in mouse Leydig cells. *Endocrinology* 152(7), 2827-36 (2011) DOI: 10.1210/en.2011-0031

48. Y. Zhang, N. Li, Q. Chen, K. Yan, Z. Liu, X. Zhang, P. Liu, Y. Chen and D. Han: Breakdown of immune homeostasis in the testis of mice lacking Tyro3, Axl and Mer receptor tyrosine kinases. *Immunol Cell Biol* 91(6), 416-26 (2013) DOI: 10.1038/icb.2013.22

49. N. Li, Z. Liu, Y. Zhang, Q. Chen, P. Liu, C. Y. Cheng, W. M. Lee, Y. Chen and D. Han: Mice lacking Axl and Mer tyrosine kinase receptors are susceptible to experimental autoimmune orchitis induction. *Immunol Cell Biol* (2014) DOI: 10.1038/icb.2014.97

50. M. Naito, H. Terayama, S. Hirai, N. Qu, L. Lustig and M. Itoh: Experimental autoimmune orchitis as a model of immunological male infertility. *Med Mol Morphol* 45(4), 185-9 (2012) DOI: 10.1007/s00795-012-0587-2

51. H. C. Schuppe, A. Meinhardt, J. P. Allam, M. Bergmann, W. Weidner and G. Haidl: Chronic orchitis: a neglected cause of male infertility? *Andrologia* 40(2), 84-91 (2008) DOI: 10.1111/j.1439-0272.2008.00837.x

52. L. Yu, L. Wang and S. Chen: Endogenous toll-like receptor ligands and their biological significance. *J Cell Mol Med* 14(11), 2592-603 (2010) DOI: 10.1111/j.1582-4934.2010.01127.x

53. Z. Liu, S. Zhao, Q. Chen, K. Yan, P. Liu, N. Li, C. Y. Cheng, W. M. Lee and D. Han: Roles of toll-like receptors 2 and 4 in mediating experimental autoimmune orchitis induction in mice. *Biol Reprod* 92(3), 63 (2015) DOI: 10.1095/biolreprod.114.123901

54. P. M. D'Cruz, D. Yasumura, J. Weir, M. T. Matthes, H. Abderrahim, M. M. LaVail and D. Vollrath: Mutation of the receptor tyrosine kinase gene Mertk in the retinal dystrophic RCS rat. *Hum Mol Genet* 9(4), 645-51 (2000) DOI: 10.1093/hmg/9.4.645

55. J. L. Duncan, M. M. LaVail, D. Yasumura, M. T. Matthes, H. Yang, N. Trautmann, A. V. Chappelow, W. Feng, H. S. Earp, G. K. Matsushima and D. Vollrath: An RCS-like retinal dystrophy phenotype in mer knockout mice. *Invest Ophthalmol Vis Sci* 44(2), 826-38 (2003) DOI: 10.1167/iovs.02-0438

56. A. Gal, Y. Li, D. A. Thompson, J. Weir, U. Orth, S. G. Jacobson, E. Apfelstedt-Sylla and D. Vollrath: Mutations in MERTK, the human orthologue of the RCS rat retinal dystrophy gene, cause retinitis pigmentosa. *Nat Genet* 26(3), 270-1 (2000) DOI: 10.1038/81555

57. M. Tschernutter, S. A. Jenkins, N. H. Waseem, Z. Saihan, G. E. Holder, A. C. Bird, S. S. Bhattacharya, R. R. Ali and A. R. Webster: Clinical characterisation of a family with retinal dystrophy caused by mutation in the Mertk gene. *Br J Ophthalmol* 90(6), 718-23 (2006) DOI: 10.1136/bjo.2005.084897

58. D. Prasad, C. V. Rothlin, P. Burrola, T. Burstyn-Cohen, Q. Lu, P. Garcia de Frutos and G. Lemke: TAM receptor function in the retinal pigment epithelium. *Mol Cell Neurosci* 33(1), 96-108 (2006)
DOI: 10.1016/j.mcn.2006.06.011

59. L. R. Pacione, M. J. Szego, S. Ikeda, P. M. Nishina and R. R. McInnes: Progress toward understanding the genetic and biochemical mechanisms of inherited photoreceptor degenerations. *Annu Rev Neurosci* 26, 657-700 (2003)
DOI: 10.1146/annurev.neuro.26.041002.131416

60. R. Gomes and F. Oliveira: The immune response to sand fly salivary proteins and its influence on leishmania immunity. *Front Immunol* 3, 110 (2012)
DOI: 10.3389/fimmu.2012.00110

61. J. V. Forrester and H. Xu: Good news-bad news: the Yin and Yang of immune privilege in the eye. *Front Immunol* 3, 338 (2012)
DOI: 10.3389/fimmu.2012.00338

62. D. C. Gritz and I. G. Wong: Incidence and prevalence of uveitis in Northern California; the Northern California Epidemiology of Uveitis Study. *Ophthalmology* 111(3), 491-500; discussion 500 (2004)
DOI: 10.1016/j.ophtha.2003.06.014

63. G. J. Williams, S. Brannan, J. V. Forrester, M. P. Gavin, S. P. Paterson-Brown, A. T. Purdie, M. Virdi and J. A. Olson: The prevalence of sight-threatening uveitis in Scotland. *Br J Ophthalmol* 91(1), 33-6 (2007)
DOI: 10.1136/bjo.2006.101386

64. H. Shao, T. Liao, Y. Ke, H. Shi, H. J. Kaplan and D. Sun: Severe chronic experimental autoimmune uveitis (EAU) of the C57BL/6 mouse induced by adoptive transfer of IRBP1-20-specific T cells. *Exp Eye Res* 82(2), 323-31 (2006)
DOI: 10.1016/j.exer.2005.07.008

65. J. Fang, D. Fang, P. B. Silver, F. Wen, B. Li, X. Ren, Q. Lin, R. R. Caspi and S. B. Su: The role of TLR2, TRL3, TRL4, and TRL9 signaling in the pathogenesis of autoimmune disease in a retinal autoimmunity model. *Invest Ophthalmol Vis Sci* 51(6), 3092-9 (2010)
DOI: 10.1167/iovs.09-4754

66. F. Ye, Q. Li, Y. Ke, Q. Lu, L. Han, H. J. Kaplan, H. Shao and Q. Lu: TAM receptor knockout mice are susceptible to retinal autoimmune induction. *Invest Ophthalmol Vis Sci* 52(7), 4239-46 (2011)
DOI: 10.1167/iovs.10-6700

67. F. Ye, L. Han, Q. Lu, W. Dong, Z. Chen, H. Shao, H. J. Kaplan, Q. Li and Q. Lu: Retinal self-antigen induces a predominantly Th1 effector response in Axl and Mertk double-knockout mice. *J Immunol* 187(8), 4178-86 (2011)
DOI: 10.4049/jimmunol.1101201

68. L. L. Muldoon, J. I. Alvarez, D. J. Begley, R. J. Boado, G. J. Del Zoppo, N. D. Doolittle, B. Engelhardt, J. M. Hallenbeck, R. R. Lonser, J. R. Ohlfest, A. Prat, M. Scarpa, R. J. Smeyne, L. R. Drewes and E. A. Neuwelt: Immunologic privilege in the central nervous system and the blood-brain barrier. *J Cereb Blood Flow Metab* 33(1), 13-21 (2013)
DOI: 10.1038/jcbfm.2012.153

69. A. L. Prieto, J. L. Weber and C. Lai: Expression of the receptor protein-tyrosine kinases Tyro-3, Axl, and mer in the developing rat central nervous system. *J Comp Neurol* 425(2), 295-314 (2000)
DOI: 10.1002/1096-9861(20000918)425:2<295::AID-CNE11>3.3.CO;2-7

70. D. Zhu, Y. Wang, I. Singh, R. D. Bell, R. Deane, Z. Zhong, A. Sagare, E. A. Winkler and B. V. Zlokovic: Protein S controls hypoxic/ischemic blood-brain barrier disruption through the TAM receptor Tyro3 and sphingosine 1-phosphate receptor. *Blood* 115(23), 4963-72 (2010)
DOI: 10.1182/blood-2010-01-262386

71. Q. Li, Q. Lu, H. Lu, S. Tian and Q. Lu: Systemic autoimmunity in TAM triple knockout mice causes inflammatory brain damage and cell death. *PLoS One* 8(6), e64812 (2013)
DOI: 10.1371/journal.pone.0064812

72. R. Ji, S. Tian, H. J. Lu, Q. Lu, Y. Zheng, X. Wang, J. Ding, Q. Li and Q. Lu: TAM receptors affect adult brain neurogenesis by negative regulation of microglial cell activation. *J Immunol* 191(12), 6165-77 (2013)
DOI: 10.4049/jimmunol.1302229

73. A. D. Bachstetter, B. Xing, L. de Almeida, E. R. Dimayuga, D. M. Watterson and L. J. Van Eldik: Microglial p38alpha MAPK is a key regulator of proinflammatory cytokine up-regulation induced by toll-like receptor (TLR) ligands or beta-amyloid (Abeta). *J Neuroinflammation* 8, 79 (2011)
DOI: 10.1186/1742-2094-8-79

74. I. N. Crispe: Hepatic T cells and liver tolerance. *Nat Rev Immunol* 3(1), 51-62 (2003) DOI: 10.1038/nri981

75. D. Vergani, M. S. Longhi, D. P. Bogdanos, Y. Ma and G. Mieli-Vergani: Autoimmune hepatitis. *Semin Immunopathol* 31(3), 421-35 (2009) DOI: 10.1007/s00281-009-0170-7

76. N. Qi, P. Liu, Y. Zhang, H. Wu, Y. Chen and D. Han: Development of a spontaneous liver disease resembling autoimmune hepatitis in mice lacking tyro3, axl and mer receptor tyrosine kinases. *PLoS One* 8(6), e66604 (2013) DOI: 10.1371/journal.pone.0066604

77. E. Seki and D. A. Brenner: Toll-like receptors and adaptor molecules in liver disease: update. *Hepatology* 48(1), 322-35 (2008) DOI: 10.1002/hep.22306

78. A. Angelillo-Scherrer, L. Burnier, N. Flores, P. Savi, M. DeMol, P. Schaeffer, J. M. Herbert, G. Lemke, S. P. Goff, G. K. Matsushima, H. S. Earp, C. Vesin, M. F. Hoylaerts, S. Plaisance, D. Collen, E. M. Conway, B. Wehrle-Haller and P. Carmeliet: Role of Gas6 receptors in platelet signaling during thrombus stabilization and implications for antithrombotic therapy. *J Clin Invest* 115(2), 237-46 (2005) DOI: 10.1172/JCI22079

79. H. Wang, S. Chen, Y. Chen, H. Wu, H. Tang, W. Xiong, J. Ma, Y. Ge, Q. Lu and D. Han: The role of Tyro 3 subfamily receptors in the regulation of hemostasis and megakaryocytopoiesis. *Haematologica* 92(5), 643-50 (2007) DOI: 10.3324/haematol.10939

80. H. Tang, S. Chen, H. Wang, H. Wu, Q. Lu and D. Han: TAM receptors and the regulation of erythropoiesis in mice. *Haematologica* 94(3), 326-34 (2009) DOI: 10.3324/haematol.13635

81. D. K. Graham, D. DeRyckere, K. D. Davies and H. S. Earp: The TAM family: phosphatidylserine sensing receptor tyrosine kinases gone awry in cancer. *Nat Rev Cancer* 14(12), 769-85 (2014) DOI: 10.1038/nrc3847

82. M. Shimojima, A. Takada, H. Ebihara, G. Neumann, K. Fujioka, T. Irimura, S. Jones, H. Feldmann and Y. Kawaoka: Tyro3 family-mediated cell entry of Ebola and Marburg viruses. *J Virol* 80(20), 10109-16 (2006) DOI: 10.1128/JVI.01157-06

83. K. Morizono, Y. Xie, T. Olafsen, B. Lee, A. Dasgupta, A. M. Wu and I. S. Chen: The soluble serum protein Gas6 bridges virion envelope phosphatidylserine to the TAM receptor tyrosine kinase Axl to mediate viral entry. *Cell Host Microbe* 9(4), 286-98 (2011) DOI: 10.1016/j.chom.2011.03.012

84. L. Meertens, X. Carnec, M. P. Lecoin, R. Ramdasi, F. Guivel-Benhassine, E. Lew, G. Lemke, O. Schwartz and A. Amara: The TIM and TAM families of phosphatidylserine receptors mediate dengue virus entry. *Cell Host Microbe* 12(4), 544-57 (2012) DOI: 10.1016/j.chom.2012.08.009

85. B. M. Sullivan, M. J. Welch, G. Lemke and M. B. Oldstone: Is the TAM receptor Axl a receptor for lymphocytic choriomeningitis virus? *J Virol* 87(7), 4071-4 (2013) DOI: 10.1128/JVI.03268-12

86. S. Bhattacharyya, A. Zagorska, E. D. Lew, B. Shrestha, C. V. Rothlin, J. Naughton, M. S. Diamond, G. Lemke and J. A. Young: Enveloped viruses disable innate immune responses in dendritic cells by direct activation of TAM receptors. *Cell Host Microbe* 14(2), 136-47 (2013) DOI: 10.1016/j.chom.2013.07.005

Key Words: TAM Receptor Tyrosine Kinases, Innate Immunity, Testis, Immune Privilege, Autoimmune Orchitis, Review

Send correspondence to: Daishu Han, Department of Cell Biology, PUMC & CAMS, 5 Dong Dan San Tiao, Beijing 100005, P. R. China, Tel: 86-10-69156457, Fax: 86-10-69156466, E-mail: dshan@ibms.pumc.edu.cn