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Journal of the Chinese Medical Association 78 (2015) 276–282

www.jcma-online.com

Review Article

Pathogenesis of innate immunity and adaptive immunity in the mouse model of experimental autoimmune uveitis

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Received March 31, 2014; accepted October 14, 2014

Abstract

Experimental autoimmune uveitis, a well-established model for human uveitis, is similar to human uveitis in many pathological features. Studies concerning the mechanisms of experimental autoimmune uveitis would cast a light on the pathogenesis of human uveitis as well as the search for more effective therapeutic agents. The cellular components of innate immunity include natural killer cells, gamma delta T lymphocytes, antigen-presenting dendritic cells, phagocytic macrophages, and granulocytes. It is believed that T cells are central in the generation of human uveitis. It has already become clear that $CD4^+$ effecter cells that predominantly produce interleukin-17 (the so-called Th17 cells) may play an important role in uveitis. In addition, the occurrence and recurrence of uveitis depends on a complex interplay between the elements of innate and adaptive immunity.

Keywords: adaptive immunity; experimental autoimmune uveitis; innate immunity; pathogenesis; uveitis

1. Introduction

Uveitis, an inflammatory disease that potentially causes blindness, presents a therapeutic challenge for all ophthalmologists. Knowledge of the classification and etiology of uveitis is important for the diagnosis and treatment of the disorder. The human body is often in routine contact with all kinds of pathogens, but it does not become diseased or ill, which is reflected in innate immunity. The adaptive immunity, distinguishing the foreign pathogens from the body, is able to maintain the integrity of the immune system and make appropriate responses to the peripheral environment. Dysfunction of innate and adaptive immune systems can result in unregulated, inappropriate, and detrimental autoimmune disease including uveitis. In this article, we will review an animal model of uveitis, the different roles of innate immunity and adaptive immunity, together with their interplay in the pathogenesis of uveitis.

2. Experimental autoimmune uveitis model is an effective and suggestive means for uveitis research

Uveitis, a common cause of visual impairment and blindness, is an autoimmune disorder predominantly mediated by T helper cells,[1] and is associated with chronic and recurrent ocular complications.[2] The annual incidence rate of uveitis varies between 17 cases and 52 cases per 100,000, and its prevalence varies between 69 cases and 204 cases per 100,000 populations.[3] In developed countries, uveitis affects approximately 200 per 100,000 in the population, and uveitis and its complications account for up to 35% of severe visual impairment.[4] Uveitis is the third leading cause of blindness

Conflicts of interest: The authors declare that there are no conflicts of interest related to the subject matter or materials discussed in this article.

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http://dx.doi.org/10.1016/j.jcma.2015.01.002

among Americans, where its prevalence is 204 per 100,000 persons per year.[5] In less developed countries, uveitis and its complications are even more common, affecting an estimated 714 per 100,000 and contributing to 25% of blindness.[4] Consequently, it poses a heavy burden on society and the family.[6]

According to the different anatomic locations of the inflammation, uveitis is classified as anterior uveitis, intermediate uveitis, posterior uveitis, and panuveitis. Anterior uveitis is the most common type, constituting 50–92% of all types in Western countries and 28–50% in Asia.[7] Intermediate uveitis is primarily idiopathic and bilateral in childhood and adult groups, and accounts for 6% of all uveitis cases observed over a period of 16 years.[8] Posterior uveitis is thought to comprise approximately 5% of all uveitis entities.[4] Acute anterior uveitis is a common ocular inflammatory disease that can cause severe visual impairment. In addition to recurrence, acute anterior uveitis may lead to sight-threatening complications such as cataract, macular edema, and glaucoma.[9] The intermediate and posterior uveitis are associated with a group of ocular disorders characterized by inflammation of the choroid, retina, retinal vessels, vitreous, or ciliary body that may occur in isolation, as part of a panuveitis, or in conjunction with systemic disease.[10]

The vast majority of cases of uveitis are caused by autoimmune response. There are animal models of uveitis (Table 1)[20,52,53]. However, because human pathology specimens have been unavailable, experimental autoimmune uveitis (EAU) has been established *in vivo*.[11] EAU is a mature animal model that can mimic human uveitis.[12] It can be manipulated by immunization with several retinal autoantigens, of which retinal S-antigen (S-Ag) and interphotoreceptor retinoid binding protein (IRBP) are featured (Tables 2 and 3)[15,54–61]. Unfortunately, most of these models display an acute and monophasic disease course with spontaneous recovery, raising questions about how well laboratory observations acquired from such studies reflect the actual situation in the human disease. Because recurrent uveitis poses the highest risk for ocular complications in human disease that could cause blindness, availability of a chronic and/or relapsing animal model would be most helpful for dissecting the disease pathogenesis. A chronic recurrent uveitis model was induced in the Lewis rat by adoptive transfer of T cells specific for IRBP peptide (sequence of 1177–1191 of bovine IRBP protein, R16).[13,14] The disease is characterized by a chronic recurrent pattern of uveitis, with an unpredictable frequency and duration of remission and relapses.[14] The clinical symptoms started 3–5 days after transfer, and manifested in multiple episodes, each lasting 1–7 days, followed by varying periods of remission. Neither the duration of a single disease peak nor the interval between episodes was predictable. In addition, the right and left eyes of a single recipient often showed a different rhythm of relapse, similar to the situation often seen in the human disease. Given that a large number of transgenic and knockout mice are available on the C57BL/6 background, many studies have chosen to use the C57BL/6 mouse. Unfortunately, C57BL/6 mice only develop very weak EAU after immunization with IRBP1–20. The induced disease occurred at a low incidence with mild inflammation and a short duration (average score of 0.5 out of maximal 4).[15,16] The availability of a reproducible model of uveitis in the C57BL/6 mouse is particularly desirable. When T cells are isolated from the immunized mice and adoptively transferred to a naïve C57BL/6 mouse, the recipient develops a much more severe disease, with an average score of 2–3 and duration of at least 60 days. Similar to relapsing uveitis in Lewis rat, the incidence, severity, and duration of disease were dependent on the number and activation status of the injected T cells.[17] In

Table 1
Major animal models of uveitis.

Animals and types of model	Examples of models	Characters	Refs
Rat			
Immunization with retinal antigen in CFA or adoptive transfer of T cells from immunized donors to naïve recipients	Arrestin-induced model in the Lewis ret. Many other retinal and choroidal (melanin) antigens are also uveitogenic in Lewis rat	Was the major EAU model until the mouse model was reported in 1988. Nowadays, it is used by relatively few groups. Generally, it mimics the acute inflammation in anterior	52,53
Mouse			
Immunization of wild type mice with ocular antigen in CFA or adoptive transfer of immune cells (or cell lines) from immunized donors to naïve recipients	EAU is induced in B10.RIII, B10.A and C57BL/6 mice with IRBP	TB in CFA provides innate signals that polarize autoimmune lymphocytes toward a proinflammatory phenotype. Generally, it is a monophasic and acute form of posterior uveitis; transient anterior uveitis.	20,52,53
Spontaneous uveitis	T cell receptor transgenic (R161H) mice in IRBP	Spontaneous uveitis can start at early age, and has minimal anterior chamber involvement; Generally, it is a chronic form of posterior uveitis	20
	Spontaneous uveitis in Autoimmune Regulator-deficient mice directed at IRBP	Spontaneous uveitis can start at early age, and lacks anterior chamber involvement. Generally, it is a chronic form of posterior uveitis	20

CFA = complete Freund's adjuvant; EAU = experimental autoimmune uveitis; IRBP = interphotoreceptor retinoid binding protein; TB = tuberculin.

Table 2
Retinal protein-derived peptides pathogenic for Lewis rats.

Source	Position	Amino acid sequence	Refs
Bovine S-Ag	333–352	LTVSGL LGELTSSEVATEVP	54
Human S-Ag	181–200	VQHAPLEMGPQPRAEATWQF	55
	(343–356)		54
Bovine IRBP	1177–1191	ADGSSWEGVGVVPDV	56
	271–283	SQTWEGSGVLPCV	57
	1158–1180	HVDDTDLYLTIPTARSVGAADGS	56
Human IRBP	521–540	YLLTSH RTATAAEEFAFLMQ	58

IRBP = interphotoreceptor retinoid binding protein; S-Ag = S-antigen.

addition, R161H mice can develop a high incidence of moderate to severe spontaneous uveitis pathology by 2–3 months of age.[18] Autoimmune regulator deficient (AIRE$^{-/-}$) mice can induce EAU.[19] Moreover, spontaneous mice can develop a chronic-progressive disease, with a significant recovery of visual function compared with IRBP-immunized B10.RIII mice.[20] The clinical heterogeneity of uveitis as well as the finding of different pathological patterns suggest that uveitis may be a spectrum of diseases that may represent different pathological processes.

3. Pathogenesis of innate immunity in uveitis

Innate immunity is an evolutionarily conserved defense mechanism capable of fighting a diverse threat of viral, prokaryotic, and eukaryotic parasites and pathogens in plants and invertebrate animals.[21] An innate immune system provides an immediate host immune response to infectious agents and relies on the expression of germline-encoded receptors for their detection.[22] A variety of circumstantial observations suggest that the innate immune system is very important in the development of uveitis.

3.1. Natural killer T lymphocytes (natural killer T cells)

Natural killer T (NKT) cells are a heterogeneous population of unconventional T cells that express markers of NK cells and T cell receptors (TCRs) and possess some of the properties of NK cells and T cells, and are also a kind of specific T lymphocyte subset. NKT cell subsets with different functions exist in humans and mice, including classical (type I) invariant and other CD1d-dependent (type II) NKT cells, and also CD1d-independent (NKT-like) T cells.[23] NKT cells are more prevalent in the liver than in other organs, comprising up to 30% of the intrahepatic lymphocytes in mice.[24] The stability of NKT cells plays a role in the control of various autoimmune diseases. Recently, it has been observed that NKT cells present a wide range of responses in their involvement in regulating the human immune system.[25] NKT cells have also been shown to have the ability to resist the virus and tumor, and contribute to the regulation of autoimmune diseases.[26] Innate immune cells, NKT cells, and macrophages not only influence inflammatory tissue damage but also participate in T lymphocyte responses to induce uveitis.[27] There is an increasing amount of evidence showing that NKT cells are involved in the regulation of the adaptive immune response as well.[28] In our previous study, we explored the diverse roles of NKT cells in the liver and spleen and found that liver-derived NKT cells could efficiently inhibit Th1 and Th17 differentiation, whereas the function of spleen-derived NKT cells was less potent. Meanwhile, the occurrence of the peak ratios of NKT cells/T cells in the spleen and liver was markedly asynchronous after immunization. Moreover, different methods of immunization could result in different immune responses in mice. Furthermore, the memory response was also found in the generation of NKT cells in mice when they received the same antigen. These results indicated that there is diversity in the functional roles of NKT cells in the spleen and liver in mice with EAU.[29]

Table 3
Susceptibility of different mouse strains to IRBP-induced EAU.

Strain	Position	Amino acid sequence	Refs
B10.RIII	161–180	SGIPYIISYLHPGNTILHVD	59
	171–190	HPGNTILHVDTIYNRPSNTT	60
B10.A	201–216	ADKDVVVLTSSRTGGV	61
C57BL/6	1–20	GPTHLFQPSLVLDMAKVLLD	15
	461–480	LRHNPGGPSSAVPLLLSYFQ	60
	651–670	LAQGAYRTAVDLESLASQLT	60

EAU = experimental autoimmune uveitis; IRBP = interphotoreceptor retinoid binding protein.

3.2. Gamma delta T lymphocytes

Gamma delta T cells were first described as peripheral blood lymphocytes expressing CD3$^+$, a commonly used T cell marker, but not alpha beta TCRs. Gamma delta T cells possessing surface receptors are a unique phenotype and the main function of lymphocyte subsets in innate immunity.[30] Studies have shown that gamma delta T cells act to "bridge the gap" between innate and adaptive immunity[31] or to regulate the intensity of the adaptive immune response.[32] There is also evidence that different gamma delta T cell subsets have different immunoregulatory effects.[33,34] It has been shown that *in vitro* activation of IRBP-specific T cells from C57BL/6 mice immunized with an uveitogenic IRBP peptide (IRBP1–20) under Th17-polarizing conditions is associated with increased expansion of T cells expressing the gamma delta TCR. It has also been shown that highly purified alpha beta or gamma delta T cells from C57BL/6 mice immunized with IRBP1–20 produced only small amounts of interleukin (IL)-17 after exposure to the immunizing Ag *in vitro*, whereas a mixture of the same T cells produced significantly increased amounts of IL-17. IRBP-induced T cells from IRBP-immunized TCR-delta$^{-/-}$ mice on the C57BL/6 genetic background produced significantly lower amounts of IL-17 than did wild-type C57BL/6 mice and had significantly decreased EAU-inducing ability. However, reconstitution of the TCR-delta$^{-/-}$ mice prior to immunization with a small number of gamma delta T cells from IRBP-immunized C57BL/6 mice restored the disease-inducing capability of

their IRBP-specific T cells and greatly enhanced the generation of IL-17$^+$ T cells in the recipient mice. Our study suggests that gamma delta T cells are important in the generation and activation of IL-17-producing autoreactive T cells and play a major role in the pathogenesis of EAU.[35]

There are some cells and proteins in the body that are involved in uveitis of innate immunity, for example, dendritic cells,[36] macrophages,[16] complement,[37] and TLRs[38] (Table 4)[27,29,33,36–38].

4. Etiology of adaptive immunity in uveitis

The mechanism of adaptive immunity has added to the human immune system a specific recognition of carbohydrates, lipids, pathogenic proteins, and nucleic acids in its effort to mount an immune defense and defy their evasion strategies and attack against the ever-growing pool of disorders.[21]

The uveitogenic T cells that mediate EAU were commonly assumed to be exclusively CD4$^+$. The involvement of both CD4 and CD8 autoreactive T cells in autoimmune diseases has been well established recently. Recent studies have also shown that a specific autoreactive T cell subset that produces IL-17, but not interferon (IFN)-γ or IL-4, is crucially involved in the pathogenesis of autoimmune diseases. We try to illustrate the uveitogenic role of CD8 and IL-17$^+$ uveitogenic T cells.

4.1. CD8 uveitogenic T cells

CD4$^+$ are commonly proposed to be exclusive in the uveitogenic T cells that modulate EAU. Our data revealed that even if all the long-term cultured uveitogenic T cell of rat lines particularly for R16 expressed CD4, as many as 40% of the freshly prepared R16-specific uveitogenic T cells from Ag-immunized rats were CD8$^+$ alpha beta TCR$^+$. The CD8 T cells were highly purified and antigen-specific CD8$^+$ R16-specific T cells that were capable of producing uveitis by means of transfusion into naive rats. Furthermore, compared to their CD4$^+$ counterparts, CD8$^+$ uveitogenic T cells were more fully prepared to switch phenotype to or from TCR$^-$CD8$^-$CD4$^-$ when they were activated *in vivo* or *in vitro*.[39]

Table 4
Function of innate immunity in uveitis.

Cells	Functions	Refs
NKT cells	Different derived NKT cells exhibit prominently inhibitory influence on the development of EAU	29
	Different derived NKT cells could exert different immune responses to EAU	29
	Possess diversity in the spleen and liver in EAU mice	29
Gamma delta T lymphocytes	In the generation and activation of IL-17-producing autoreactive T cells and play a major role in the pathogenesis of EAU	33
	Have a proinflammatory effect in EAU	33
	Expressing Vγ4 TCR segments in EAU	33
Macrophages	Participant in T lymphocyte responses to induce uveitis	27
Dendritic cells	Activated dendritic cells into the retina by local injury promoted the pathogenesis of EAU	36
Complement	Decrease the inflammatory response	37
TLRs	Contribute to the pathogenesis of uveitis	38

EAU = experimental autoimmune uveitis; IL = interleukin; NKT = natural killer T; TCR = T cell receptor; TLRs = Toll-like receptors.

Autoreactive CD8 T cells were also abundant in B10.RIII mice, an EAU-susceptible strain, immunized with the uveitogenic peptide IRBP161–180.[40] Different from CD4 autoreactive T cells, the growth factors produced by activated CD8 autoreactive T cells were rather limited.[41] For this reason, the activation and expansion CD8 T cell would be aborted in the absence of exogenously supplied growth factor(s), whereas the growth and expansion of triggered CD8 autoreactive T cells could be supported by a series of cytokines. Besides the factors produced by activated CD4 autoreactive T cells, other factors produced by nonlymphoid cells (e.g., IL-7, IL-15), retinal pigment epithelial (RPE) cells, as well as unidentified factors in the culture supernatants of astrocytes were capable of supporting the CD8 autoreactive T cells as well. Even though the response of CD8 T cell *in vitro* could be augmented by several cytokines, different cytokines seem to act on different CD8 subsets or activation/differentiation phases of CD8 autoreactive T cells. For this reason, cytokines, such as IL-7, were proposed to support the proliferation and survival of CD8 IRBP-specific T cells, whereas others only had a growth-promoting effect.

Additionally, a previous study, by which the role of the CD8 IRBP-specific T cells in the etiology of EAU could be further corroborated, demonstrated that the susceptibility of the β2-microglobulin$^{-/-}$ mouse to the induction of EAU by adoptive transfer of IRBP-specific T cells from C57BL/6 mice was substantially decreased.[42]

4.2. IL-17$^+$ uveitogenic T cells

Recent investigations have shown that a specific autoreactive T cell subset that produces IL-17 instead of IFN-γ and IL-4, played a key role in the etiology of autoimmune disorders, including experimental autoimmune encephalomyelitis, rheumatoid arthritis, and other allergic diseases, especially in the chronic phase.[43–45] In order to determine the role of IL-17$^+$ T cells in the generation of EAU and the interrelationship between previously characterized uveitogenic T cell subsets and IL-17$^+$ T cells, we investigated the involvement and the pathologic function of IL-17$^+$ T cells in EAU. By making a comparison of the pathogenic effect between IL-17$^+$ and nonspecific IL-17$^+$ T cells specific for the uveitogenic antigen, the event whether IL-17 was expressed by CD4 autoreactive T cells exclusively or by CD8 autoreactive T cells, which we were even more interested in, was further determined. Our data revealed that, in EAU, the capability of CD4 and CD8 autoreactive T cells were equal in expressing IL-17. IL-17

would be preferentially expressed by IRBP-specific T cells when they were expanded by IL-23, whereas IFN-γ-expressing cells were dominant when the T cells were cultured with IL-2. Both sets of expanded T cells were uveitogenic. The results of the comparison between IL-17$^+$ T cells elicited by antigen-specific stimulation *in vitro* and those elicited by antigen-nonspecific activation (anti-CD3 antibody) revealed that only antigen-specific IL-17$^+$ T cells were uveitogenic. More interestingly, the activation of IL-17-producing T cells were markedly enhanced by the ligation of TLRs both *in vivo* and *in vitro*.[46]

IL-17$^+$ T cells would accumulate in the inflamed eye in uveitis patients, and the number of such T cells usually correlated with the severity of the induced disease. Thereafter, intraocular injection of anti-IL-17 markedly attenuated the severity of disease, and the number of infiltrating cells in the eye was significantly decreased in the treated mice. And the activated retinal astrocytes (RACs), other than RPE, would contribute to the increased proportion of intraocular IL-17$^+$ T cells.[47]

Together with the IL-23/IL-17 basic study in EAU, the role of IL-23 and IL-17 is also discussed in Vogt−Koyanagi−Harada syndrome during the clinical study of uveitis. The expression of IL-23 and IL-17 are increased in patients, and IL-23 can promote the production of IL-17 in peripheral blood mononuclear cells. A previous study demonstrated that the IL-23/IL-17 pathway might play a key role in the etiology of Vogt−Koyanagi−Harada syndrome, and this result has been further corroborated by an investigation of Behcet's disorder.[48]

5. Interplay of innate and adaptive immunity in uveitis

Many of the diseases that afflict mankind are now thought to be the result of dysfunctional innate and/or adaptive immune responses.[49] In some cases, the adaptive immune elements restrain innate immune responses. In other cases, the combination of innate and adaptive immunity maximizes the host defense while minimizing collateral damage to the host tissues. Innate immunity generates help signals in the damaged tissues, whereas adaptive immunity provides specific responses to the insult that directly attack the pathogenic process or recruit other powerful innate effector cells that, although not specific by themselves, can act specifically by their selective recruitment.[21] Little is actually known about innate-adaptive connections.[50] However, the mechanisms by which the innate immune system instructs and directs adaptive immune responses are becoming increasingly clear.[51] Interactions between innate and adaptive immunity can result in harmful immunologic responses.[51] The nexus of the innate and adaptive systems involves many secrets even now, and both innate and adaptive immunologists are finally united in their desire to uncover them, working across a gap that is ever narrowing.[50] It is clear from the discussion in this section that further evaluation of the relationship between the innate and the adaptive arms of the immune system will provide a significantly deeper insight into the mechanisms of uveitis as well as result in better therapeutic approaches.

6. Future perspectives

In this article, we have introduced important components of an animal model of uveitis. EAU is an excellent animal model for studying the pathogenesis of autoimmune diseases. Better understanding of the pathogenesis of uveitis may help clinicians manage patients with inflammatory ocular diseases, and further enable different uveitis entities to be effectively compared.

EAU is regarded as an acute, monophasic disease. Although EAU models help to shed light on the mechanisms driving human disease, it is impossible to comprehensively imitate human uveitis. Therefore, it is necessary to establish a far better model to mimic human uveitis. The role of Th17 and IL-17 in the pathogenesis of uveitis remains undefined in some aspects. The innate and adaptive immune systems form one integrated defense network. The interplay between the two systems will become more meaningful when their mechanisms are identified completely. EAU has also served as a useful template for novel therapeutic approaches. By focusing on EAU, different pathogenesis points provide clinicians with some valid therapeutic targets for human uveitis. However, continuation of the study would allow us to obtain much-needed information for designing new and better therapies for control and cure of such diseases.

Acknowledgments

The article was supported by the National Natural Science Foundation of China (81072961 and 81100658) and the Natural Science Foundation of Shandong province (ZR2010HM048).

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