

Immunopathogenesis of ocular allergy: a schematic approach to different clinical entities

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Purpose of review

The immunopathogenesis of ocular allergic disorders is generally related to the specific immunoglobulin E-mediated mast cell activation and the following cascade of inflammatory mediators. Seasonal and perennial allergic conjunctivitis, however, are the only ocular diseases to involve solely type I hypersensitivity. The other main forms, vernal and atopic keratoconjunctivitis, have a more complex immunological basis and a chronic inflammatory component. Involvement of inflammatory cells, particularly eosinophils and T cells, cytokines and proteases can lead to more serious corneal damage with vision-threatening potential.

Recent findings

Experimental allergic conjunctival models and clinical research studies have shown that T helper type 2-related mechanisms are definitely involved in the sensitization phase of ocular allergy, however, both T helper type 1 and type 2 cytokines are overexpressed in the active disease, contributing to the development of ocular inflammation.

Summary

A review of the recent literature allows us to better understand the mechanisms involved in the development of ocular allergy and to guide us toward a more schematic approach, which could possibly be useful in forming a new classification, standardizing clinical phases and individuating new treatment targets.

Keywords

allergic conjunctivitis, immunopathogenesis, T helper type 2 cytokines

Abbreviations

AKC	atopic keratoconjunctivitis
CCR	CC chemokine receptor
GPC	giant papillary conjunctivitis
Ig	immunoglobulin
IFN	interferon
IL	interleukin
MCP	monocyte chemoattractant protein
MIP-1α	macrophage inflammatory protein 1 α
PAC	perennial allergic conjunctivitis
SAC	seasonal allergic conjunctivitis
Th	T helper
TNFα	tumor necrosis factor α
Treg	T regulatory
VKC	vernal keratoconjunctivitis

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Introduction

Ocular allergy is a disease affecting the entire ocular surface including conjunctiva, lids, cornea, lachrymal gland and tear film. The external eye represents an ideal site for immediate hypersensitivity reactions, because of the high number of mast cells in the eyelids and bulbar conjunctiva, as well as for the potential local synthesis of immunoglobulin E (IgE) [1]. This disease ranges in severity from mild forms, which can still interfere significantly with quality of life, to severe cases characterized by potential impairment of visual function. The term allergic conjunctivitis, however, refers to a collection of hypersensitivity disorders that affect the lid, conjunctiva or cornea. Various clinical forms are included according to the traditional classification of ocular allergy: seasonal (SAC) and perennial allergic conjunctivitis (PAC), vernal keratoconjunctivitis (VKC), atopic keratoconjunctivitis (AKC), giant papillary conjunctivitis (GPC) and contact or drug-induced dermatoconjunctivitis (CDC). The criteria for the classification of ocular allergy may change if we consider different aspect of the disease, clinical signs and symptoms, the length of the disease, or the immunopathogenesis. For example, a conjunctivitis can be classified as 'mild', 'moderate' or 'severe' depending on the character of disease presentation or, according to onset and duration, it can be classified as 'acute' or 'chronic' and 'recurrent', or as 'follicular' and 'papillary conjunctivitis', 'cicatrising' and 'noncicatrising', emphasizing the predominant clinical presentations. In 2001, the European Academy of Allergology and Clinical Immunology (EAACI) suggested a new classification for allergic conjunctivitis, dividing the conditions into IgE-mediated and non-IgE-mediated conjunctivitis, thus

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Table 1 Clinical and immunopathological classification of ocular allergy

	IgE mediated	IgE and non-IgE mediated	Non-IgE mediated
Intermittent	SAC		
Persistent	PAC	VKC	GPC
Chronic		AKC	CDC

IgE, immunoglobulin E; SAC, seasonal allergic conjunctivitis; PAC, perennial allergic conjunctivitis; VKC, vernal keratoconjunctivitis; GPC, giant papillary conjunctivitis; AKC, atopic keratoconjunctivitis; CDC, contact dermatitis.

trying to have a more schematic immunopathological approach to the classification. IgE-mediated conjunctivitis can be divided into intermittent and persistent conjunctivitis. Persistent allergic conjunctivitis was classified into VKC and AKC. This classification, however, has limitations and may create more confusion. For example, contact blepharitis or CDC is a non-IgE-mediated form of localized contact dermatitis, but immunologically different from VKC or AKC [2**]. Contact lens-related GPC should be considered as non-IgE mediated, mechanically related to the lens micro-trauma, which, however, shares some immunopathological aspects with VKC. In 2006, the International Ocular Inflammation Society (IOIS) proposed a more comprehensive classification for conjunctivitis and blepharitis, including ocular allergy in the 'non infectious, immunomediated' conjunctivitis and including both the 'IgE-mediated' SAC and PAC and the 'non-IgE-mediated' VKC and AKC (Table 1).

In SAC pathological changes, such as increased mast cell activation, the presence of migratory inflammatory cells and early signs of cellular activation at the molecular level are minimal. In PAC, these changes are more pronounced, in line with the increased duration of allergenic stimulation. In more chronic forms of allergic conjunctivitis, such as VKC in children, and AKC in adults, a persistent state of mast cell, eosinophil and lymphocyte activation are more evident, associated with a switching from connective-tissue to mucosal-type mast cells, an increased involvement of corneal pathology, tissue remodelling and fibrosis [3,4]. In SAC and PAC, the cornea is never involved, suggesting that inflammatory cell and structural cell activation may have additional triggers in VKC and AKC. In contrast, in GPC the conjunctival remodelling is associated to a Th2 cytokine profile without clear immunological sensitization and without corneal involvement.

IgE mediated: seasonal and perennial allergic conjunctivitis

The ocular allergic response results from the exposure of the conjunctiva to an environmental allergen and the binding with specific IgE on the conjunctival mast cells. Activation of these cells induces the release of preformed

inflammatory mediators localized in specialized granules and the de-novo synthesis and secretion of cytokines, chemokines and eicosanoids. This immediate or early response lasts clinically 20–30 min, as demonstrated by the specific conjunctival allergen challenge. It induces enhanced tear levels of histamine, tryptase, prostaglandins, leukotrienes, and the recruitment of inflammatory cells [3].

Conjunctival mast cells are 100% tryptase positive and chymase positive (connective type mast cells) and express interleukin (IL)-4. This cytokine plays a key role in allergy promoting T-cell growth, inducing IgE production from B cells, upregulating the adhesion molecules and regulating T helper type 2 (Th2) cell differentiation [4]. IL-4 together with tumor necrosis factor α (TNF α) is a promoter of eotaxin expression and secretion from corneal keratocytes and conjunctival fibroblasts, but not from epithelial cells [5].

Activated mast cells release several cytokines, however, stimulated epithelial cells and fibroblasts can produce proinflammatory cytokines and chemokines, such as RANTES, monocyte chemoattractant protein (MCP), IL-8, eotaxin, and macrophage inflammatory protein 1 α (MIP-1 α) [6]. Recently it has been shown that MIP-1 α may have a relevant role as a costimulatory signal for mast cell degranulation in the mouse conjunctiva and consequently is necessary for inducing the acute-phase response. Antagonizing MIP-1 α interaction with its receptor, the CC chemokine receptor 1 (CCR1), or blocking the signal transduction cascade from CCR1 may be a new target for the treatment of ocular allergy [7].

The late phase conjunctival allergic response occurs a few hours after the first mast cell activation and it is characterized by the infiltration of inflammatory cells such as neutrophils, lymphocytes, basophils and eosinophils. An increased expression of adhesion molecules such as E-selectin and intercellular adhesion molecule (ICAM)-1, are indispensable for the influx of these inflammatory cells. The adhesion molecule, very late antigen (VLA)-4 and its ligand, vascular cell adhesion molecule (VCAM)-1, are known to play a major role in the eosinophil infiltration. In fact, VLA-4-expressing cells infiltrate the conjunctiva and the interaction with its ligand is needed for the development of the experimental allergic conjunctivitis [8*].

The ratio of Th1/Th2 type cytokines plays crucial role in the allergic inflammatory process. Both types are important for the allergic reaction. In fact, although IL-12 is a typical Th1 cytokine, it was shown to be important in the development of the late phase response in the IL-12 knock-out mice model [9]. Similarly, interferon (INF)- γ promotes the severity of experimental allergic conjunctivitis in

genetically predisposed animals [10[•]], induces the expression of adhesion molecules and the development of the late phase response [11], suggesting that IFN γ may play a proinflammatory role in the allergic responses and that IFN γ -secreting cells may be important in inducing and perpetuating the late phase reaction [12,13]. This is what probably occurs in persistent and chronic conjunctival inflammations. By contrast, IFN γ downregulated the development of allergic conjunctivitis during the induction phase in the experimental model [12]. Thus, it appears that IFN γ and CD8+ T cells act as a downregulator during the induction phase of experimental conjunctivitis, but promotes its development during the active phase [14]. This was confirmed by the fact that experimental allergic conjunctivitis was attenuated when any of the IFN γ –IFN γ receptor interactions were disturbed [15[•]].

The Th1/Th2 balance depends also on the expression of intracellular regulatory signals. The suppressor of cytokines signals SOCS3 and SOCS5 are predominantly expressed in Th2 and Th1 cells, respectively, and reciprocally inhibit the Th1 and Th2 differentiation processes. SOCS3 is highly expressed in the allergic conjunctiva, and its reduction or its function inhibition clearly reduces the severity of the experimental allergic conjunctivitis. Constitutive expression of SOCS5, a specific inhibitor of IL-4 signaling, however, results in reduced eosinophil infiltration [16^{••}]. These data suggest that intracellular signals in allergic patients are different from nonallergic individuals and that negative regulation of the Th2-mediated response by dominant-negative SOCS3 and SOCS5 could be a target for therapeutic intervention in allergic diseases.

In allergic patients, the ratios of TNF α /IFN γ , IL-5/IFN γ and IL-5/IL-10 are significantly increased in SAC [17], confirming that in the IgE-mediated reaction a Th2 phenotype is predominant. It is becoming evident that T-regulatory cells (Treg) play a suppressive role in the development allergy and that modulation of Treg function may be a possible therapy for allergic patients. The role of Treg cells and regulatory cytokines such as IL-10 and transforming growth factor β (TGF β) in ocular allergy, however, is still unclear [18^{••}]. It has been shown that IL-10 and TGF β do not have immunosuppressive roles in the development of experimentally induced allergic conjunctivitis [19[•]]. Moreover, these two cytokines increase the infiltration of eosinophils into the conjunctiva during the effector phase of experimentally induced allergic conjunctivitis. Understanding this aspect may further change our approach to the classification and the treatments of ocular allergy.

Recently it has been demonstrated that α -galactosylceramide (α GalCer) activates natural killer T cells (NKT

cells) and suppresses the development of experimental airway inflammation via the upregulation of IFN- γ . In the experimental allergic conjunctivitis model, treatment with α GalCer at the time of immunization was found to significantly increase Th2 responses and markedly upregulate the severity of the ocular reaction. Treatment with α GalCer just before the antigen challenge in sensitized animals, however, significantly suppressed the disease. These data suggest that NKT cells can play a downregulatory role in the development of experimental allergic conjunctivitis [20].

Finally, the expression of epithelial cell adhesion proteins and cytoskeletal elements is downregulated in the conjunctiva of SAC patients out of season, compared with normal controls. These findings suggest that the altered expression of proteins on the ocular surface may have an important impact on the ability of the epithelium to protect itself against allergen penetration, potentially influencing the development and course of allergy [21[•]].

IgE and nonIgE-mediated: vernal and atopic keratoconjunctivitis

VKC is a chronic and severe form of ocular allergy characterized by the massive involvement of T cells, macrophages, neutrophils and eosinophils, and which can be considered as a severe clinical late phase reaction [6]. The IgE-mediated mechanism does not explain completely the severity and the clinical course of this disease, which is probably also related to T-cell-mediated responses, massive eosinophil attraction and activation, and nonspecific hypersensitivity [22].

An increased number of CD4+ T cells, Th2 cells and increased levels and expression of Th2-type cytokines have been described in the conjunctiva of VKC patients since the 1990s. Recently, more attention has been given to the role of dendritic cells in this disease. In fact, the antigen presenting cells provide an important mechanism for Th2 cell activation and further cytokine release. B7-1 and B7-2, the costimulatory molecules on antigen-presenting cells, interact with CD28 located on Th2 cells [23], activating them during the induction and effector phase. In contrast, CTLA-4 is expressed on activated T cells and transmits a negative signal, downregulating the ongoing T-cell responses upon engagement by B7-1 or B7-2 [24[•]]. Interaction of other ligands may also be crucial in the production of IgE, for example, conjunctival B cells expressing the ligands CD23, CD21 and CD40 are activated in individuals with VKC. These B cells may be responsible for the IgE production associated to VKC [25]. A direct activation of allergen-specific T cells by T-cell peptides or direct activation of dendritic cells bearing high-affinity receptors for IgE may be alternative pathways for initiating an allergic reaction in patients with and without evidence of specific IgE sensitization.

In fact, specific IgE sensitization is identified in only 50% of patients [26^{••}], suggesting that non-IgE-mediated activation pathways may be present in VKC.

The presence of Th2 cells and Th2-type cytokines has been proven and confirmed in several studies. During the active inflammatory phase of the disease, however, multiple cytokines are overexpressed and produced [27^{••}], including the typical Th1-type cytokine, INF γ [28[•]], which probably contributes to increasing the ocular inflammation, as has been shown in animal models.

The massive infiltration of inflammatory cells is typical of VKC and differentiates this disease from SAC and PAC. Chemokines such as IL-8, MCP-1, RANTES and eotaxin are actively secreted in VKC and produced by mast cells, macrophages, epithelial cells and fibroblasts [27^{••},29,30^{••}] (Table 2). Chemokine receptors, CCR3 and CXCR3, were found to be greatly upregulated in conjunctival tissues and T cells [31].

Fibroblasts appear to be a great source of chemokines, in addition to macrophages and the other inflammatory cells. In fact, in several studies, it has been shown that stimulation of corneal or conjunctival fibroblasts with TNF α alone or in combination with either IL-4 or IL-13 results in upregulation of the production and expression of eotaxin, MCP-1, RANTES, inducible protein-10, Mig and thymus and activation-regulated chemokine (TARC) [27^{••},32].

Th2-type cytokines IL-4 and IL-13 also have another important role in the pathogenesis of this disease since they stimulate the migration, proliferation and collagen production from conjunctival fibroblasts. The altered

balance between the expression of matrix metalloproteinases (MMPs) and tissue inhibitors of MMP contribute to the excessive deposition of extracellular matrix and the formation of giant papillae. It has been shown that several growth factors, including vascular endothelial growth factor, are overexpressed in VKC tissues and may be involved in tissue growth and remodeling [33–35].

The increased number of eosinophils and eosinophil-activating factors compared with SAC and PAC may contribute to the frequent corneal complication of VKC. For example, gelatinase B is secreted by eosinophils and may function with the other eosinophil products such as major basic protein and eosinophil cationic protein (ECP), to cause cellular disaggregation, epithelial desquamation and toxicity leading to corneal epitheliopathy and ulcer [36,37]. In addition, several enzymatic systems may be activated in the chronic disease contributing to cell migration, tissue damage and remodeling. In fact, metalloproteases are overexpressed and activated in VKC [35] and urokinase, an extravascular fibrinolytic system activator, is highly produced in active patients, and expressed by inflammatory cells and by conjunctival cell cultures exposed to cytokines involved in the allergic inflammation [38]. Moreover, the activity of α 1 antitrypsin, the archetype of the serine protease inhibitor, is locally reduced in VKC, creating an imbalance between protease and inhibitors, and facilitating or prolonging conjunctival inflammation [39[•]]. In fact, tear trypsin inhibitory capacity is reduced whereas tear MMP-1 and 9 activity increased [39[•]]. In addition, it has been shown that the upregulation of thymosin β 4 in the conjunctival stroma, and its peculiar localization in eosinophils and myofibroblasts, may suggest its possible role in tissue inflammation and remodeling occurring in VKC [40[•]].

Table 2 Tear mediators, cytokines and cells detected in active ocular allergies

	IgE mediated (SAC and PAC)	IgE and non-IgE mediated (VKC and AKC)	Non-IgE mediated (GPC and CDC)
Mediators	Histamine Prostaglandin D2 Leukotriens PAF ICAM	Histamine Prostaglandins Leukotriens PAF ICAM, VCAM MMPs, proteases, MBP, ECP	Prostaglandins Leukotriens ICAM
Cytokines and chemokines	IL-1, IL-4, IL-8, TNF α , IFN γ MIP-1 α	IL-1, IL-4, IL-5, IL-6, IL-8, IL-10, IL-13, TNF α , INF γ Eotaxin, MCP, RANTES, TARC, Mig	IL-1, IL-6, IL-8, TNF α , INF γ RANTES, MCP
Cells	Mast cells Neutrophils Eosinophil	Mast cells Neutrophils Eosinophils Basophils T cells Macrophages NKT	T cells Macrophages Neutrophils

AKC, atopic keratoconjunctivitis; CDC, contact or drug-induced dermatoconjunctivitis; ECP, eosinophil cationic protein; GPC, giant papillary conjunctivitis; ICAM, intercellular adhesion molecule; IFN γ , interferon γ ; IgE, immunoglobulin E; IL, interleukin; MBP, major basic protein; MCP, monocyte chemoattractant protein; MIP-1 α , macrophage inflammatory protein 1 α ; MMP, matrix metalloproteinase; NKT, natural killer T cell; PAC, perennial allergic conjunctivitis; PAF, platelet-activating factor; SAC, seasonal allergic conjunctivitis; TARC, thymus and activation-regulated chemokine; TNF α , tumor necrosis factor α ; VCAM, vascular adhesion molecule; VKC, vernal keratoconjunctivitis.

Nonspecific hypersensitivity is another typical aspect of this disease in part due to the persistent subclinical inflammation. In addition, we recently showed an increased and altered expression of muscarinic and adrenergic receptors and neurotransmitters in VKC tissues [41^{••}], explaining mucus hypersecretion, goblet cell hyperplasia and conjunctival hyperreactivity typical of this disease.

AKC is the ocular manifestation of a complex and systemic altered immune response, often associated with atopic dermatitis and with other allergic disorders, such as rhinitis and asthma. Ocular clinical expression can involve eyelids, conjunctiva and cornea, and includes different levels of severity, from mild injuries to sight-threatening complications. Similarly to VKC, its pathogenesis involves multiple factors, including genetic background, antigen sensitization, Th2 type cells and cytokines, neuroendocrine influences and tissue hyperreactivity.

The AKC signs and symptoms can be related to mast cell, T-cell and eosinophil activation as in the other IgE-mediated ocular diseases. While high serum total IgE level is a common laboratory test finding in AKC, however, almost 45% of patients do not have any specific sensitization shown by skin tests or specific serum IgE analysis. Conversely, when there is a positive result in allergological screening, specific IgEs are more often directed against multiple different allergens [42].

Higher levels of IFN- γ , TNF- α , IL-2, IL-4, IL-5 and IL-10 than controls were detected in the tears of these patients, suggesting that both Th1 and Th2 responses may be activated [27^{••},43,44] (Table 2).

As in VKC, the role of chemokines and their receptors as regulators of cell recruitment has been highlighted. Eotaxin and its receptor, CCR3, were detected in the tears and mucus of AKC patients [45]. TARC/CCL17 and the receptors, CXCR4 and CCR4, have been found highly expressed in giant papillae and correlated with IL-4 and IL-13 expression [46]. Moreover, in the same study, cultured human conjunctival fibroblasts expressed stromal cell derived factor-1 (SDF-1/CXCL12), a chemokine initially characterized as a growth factor for T and pre-B lymphocytes, and which is also a costimulatory factor for CD4⁺ T-cell activation, and an angiogenic factor [46]. Similarly, macrophage migration inhibitory factor, a multipotent activating chemokine, was significantly increased in patients with severe AKC and atopic dermatitis than in controls [47], suggesting that all these factors recruit a large number of mature and immature leukocytes and may stimulate the formation of giant papillae.

AKC is a chronic disease associated with qualitative or quantitative alterations in the mucous component of the

tear film, causing mucus discharge, epithelial disease and dry eye signs and symptoms. It has been shown that conjunctival squamous metaplasia and goblet cell loss in AKC are associated with altered expression of mucin subtypes (a decrease in mucin 5AC and upregulation of mucin 1, 2 and 4 gene expression), and may be responsible for the lower stability and wettability of the lacrimal film in this disease [48^{••},49]. A significant epithelial disease was also correlated with a low corneal sensitivity, indicating the relevance of the trophic effects of corneal nerves for the health of the ocular surface.

Staphylococcus aureus colonization is common in AKC, potentially activating epithelial cells via toll-like receptor 2 (TLR-2) [50]. No relation was found between the severity of AKC and the presence of microorganisms, however, despite the fact that *S. aureus* was frequently isolated from the lid margin [44]. It is possible that mechanisms related to activation innate immunity receptors (TLRs) play an active role in the chronic ocular inflammatory response [51].

NonIgE-mediated: giant papillary conjunctivitis

GPC is not strictly an allergic disease, but an inflammatory disorder that typically leads to the formation of giant papillae (diameter > 0.3 mm) on the superior conjunctival tarsum, usually with no significant corneal involvement. It is determined by two factors: a repeated mechanical stimulus and an abnormal conjunctival immune response.

The micro-trauma of the conjunctiva is more often caused by all types of contact lenses, but also by ocular prostheses, exposed sutures, elevated corneal deposits and extruded scleral buckles. Contact lens design, polymer constitution, surface features, replacement intervals, wearing period and fitting characteristics can influence the development and the prolongation of this disease that causes contact lens intolerance. The mechanical conjunctival and corneal irritation is supposed to alter local inflammatory mediators, such as IL-8, and to stimulate recruitment of dendritic cells, yet enhancing antigen presentation to T cells and immune responsiveness [52,53].

Moreover, an altered tear secretion is reported in many GPC patients and should be an adjuvant feature in the development of conjunctival alterations, by reducing tear clearance of the surface epithelium and facilitating concentration of inflammatory mediators and adhesion of antigens [54].

The immune response seems to be primarily directed against the proteins or the protein residues deposited on the lenses more than to the lens polymer itself, even if a role is also hypothesized for components of lens care

Table 3 Cells and mechanisms involved in ocular allergic diseases

	IgE	Mast cells	Eosinophils	Th1 response	Th2 response	Corneal involvement
SAC	+++	+++	+	—	+	—
PAC	+++	++	+	—	+	—
VKC	+	++	+++	+	+++	+++
AKC	+	++	+++	++	+++	+++
GPC	—	+	—	+	+	—
CDC	—	—	+	+++	—	—

AKC, atopic keratoconjunctivitis; CDC, contact or drug-induced dermatitis; GPC, giant papillary conjunctivitis; IgE, immunoglobulin E; PAC, perennial allergic conjunctivitis; SAC, seasonal allergic conjunctivitis; Th, T helper; VKC, vernal keratoconjunctivitis

systems and bacteria. The inflammation in GPC is apparently similar to the immune reaction developed in VKC, however the recent literature strongly differentiates the pathogenesis of these two diseases.

Although some histopathological and cytological aspects are similar, the tear cytokine profiles in GPC and VKC are different. IL-6, its soluble receptor (IL-6sR) and tissue inhibitor of metalloproteinase-2 were the only factors significantly increased compared with normal tears, both in GPC and VKC [55], suggesting that they may be involved in giant papillae formation in both diseases.

Even if eosinophils may be present in histological inflamed GPC conjunctiva, they do not seem to play a major role in GPC pathogenesis, since eotaxin and ECP levels are not increased in affected patients. Although the numbers of mast cells and lymphocytes are increased in GPC tissues, eotaxin-mediated eosinophil recruitment and eosinophil activation do not seem to have a major role in the immunopathology of GPC [3,55,56].

Contact blepharitis or dermatitis

CDC involves the skin of the eyelid or conjunctiva. It is related to contact T-cell-mediated delayed hypersensitivity reaction to haptens (incomplete antigens), which become immunogenic only after they bind to tissue protein. The antigen is captured by Langerhans cells of the eyelid skin or the conjunctiva and presented to T-helper lymphocytes in the regional lymph nodes. The sensitized T-cells react by secreting cytokines and several chemotactic factors, resulting in recruitment and activation of inflammatory cells and resident cells.

Conclusion

IgE and non-IgE-mediated mechanisms are involved in the development of ocular allergic diseases (Table 3). The multiple mediators, cytokines, chemokines, receptors, proteases, growth factors, intracellular signals, regulatory and inhibitory pathways, and other unknown factors and pathways are differently expressed in the different allergic disorders, inducing the different clinical aspects. A better understanding of these mechanisms will be useful for new classification criteria and new therapeutic strategies.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 456).

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