Complement in skin diseases

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KEY WORDS

complement, autoimmunity, deficiency, dermatologic diseases, bullous dermatoses, psoriasis

SUMMARY

Complement is one of the most important mechanisms of natural resistance preventing infections in humans and animals. It is actively involved in the pathogenesis of several diseases, including skin diseases, characterized by the presence of autoantibodies, foreign microorganisms, altered tissue cells, and the presence of mannan. Complement is intended to kill invading microorganisms but it can also destroy the organism's own damaged or altered cells. It is characterized by vigorous activity and is also potentially harmful for the host if triggered in its own body. This review discusses the significance of complement activation for emerging skin diseases and highlights the importance of serological laboratory tests for the detection of complement system activity alterations in skin diseases such as pemphigus vulgaris, bullous pemphigoid, herpes gestationis, dermatitis herpetiformis, porphyria, urticaria, angioedema, cutaneous vasculitis, systemic lupus erythematosus, partial lipodystrophy, lichen planus, xeroderma pigmentosum, psoriasis, and recurrent cutaneous infections. Finally, we draw attention to the current potential for treating these diseases with complement inhibitors.

Introduction

It has already been known for decades that the complement system plays a significant role in many skin diseases (1–3). Changes in the function of the overall complement system or individual components of it have been described for various autoimmune conditions and complement deficiency, and are also typical of some dermatologic diseases (3–6). It is thought that complement is involved in blistering skin diseases such as pemphigus vulgaris, bullous pemphigoid, herpes gestationis, dermatitis herpetiformis, and porphyrias. In these diseases, the presence of autoantibodies, defects of complement components, alteration of specific enzymes increasing levels of IL-1 alpha and TNF-alpha, and other factors influencing the complement system function and serving as initiators of disease have already been demonstrated (7–9). Complement activation is also involved in diseases involving injured vessels such as urticaria, angioedema, and cu-

taneous vasculitis (10, 11). The third group is skin diseases connected with a deficiency of the complement system (12, 13). Congenital or acquired complement deficiencies are associated with angioedema (C1-INH deficiency), discoid lupus, cutaneous vasculitis and systemic lupus erythematosus (C1, C2, C3, or C4 deficiency), partial lipodystrophy (presence of C3NeF), lichen planus (C4 deficiency), xeroderma pigmentosum (C8 deficiency), and recurrent cutaneous infections (deficiency of CR3) (11, 14, 15). Complement is also involved in psoriasis (16). The aim of this paper is to present information on how complement system activity is altered in the serum and plasma of patients with skin disease.

Structure and function of the complement system

The complement system is one of the most important mechanisms of natural resistance. It is composed of around 34 individual protein components. Some of them have enzymatic activity and are able to cleave other components into smaller products with biologically significant functions. The complement system is activated through three pathways: classical, alternative, and lectin. They are ontogenetically of different ages, the alternative pathway being the oldest and classical the youngest. It is significant for all three pathways that they activate (cleave) the central component of complement cascade C3 and form a unique terminal or lytic complex, which is responsible for damaging the target structure. The terminal complex is the most important product of complement activation and it acts to destroy the invader. If the foreign structure happens to be near normal tissue, or if normal tissue is altered to be similar to the foreign antigen, complement is activated and it destroys the modified constituent. In non-pathological conditions, the complement system is precisely regulated to prevent the occurrence of inflammation and possible self-destruction of the organism.

Not only the terminal complex, but also some cleavage products of the complement components are biologically important. The most important are cleavage products of C5, C5b, and C5a. C5b is the basis for the formation of membrane-bound lytic complex and C5a is the most powerful chemo-attractant for neutrophils and macrophages. In addition, in some conditions C5a can activate mast cells and start an anaphylactic reaction. Other important cleavage products include C3a, C3b, iC3b, C3d/dg, C4d, Ba, and Bb. These can construct new important complexes such as C4a2b – C3 convertase of the classical pathway, C3bBb – C3 convertase of the alternative pathway, C4a2b3b – C5 convertase of the classical pathway, C3bBb3b – C5 converstase of the alternative pathway, and C5b-9 or membrane attack complex (MAC), also known as lytic complex (Fig. 1).

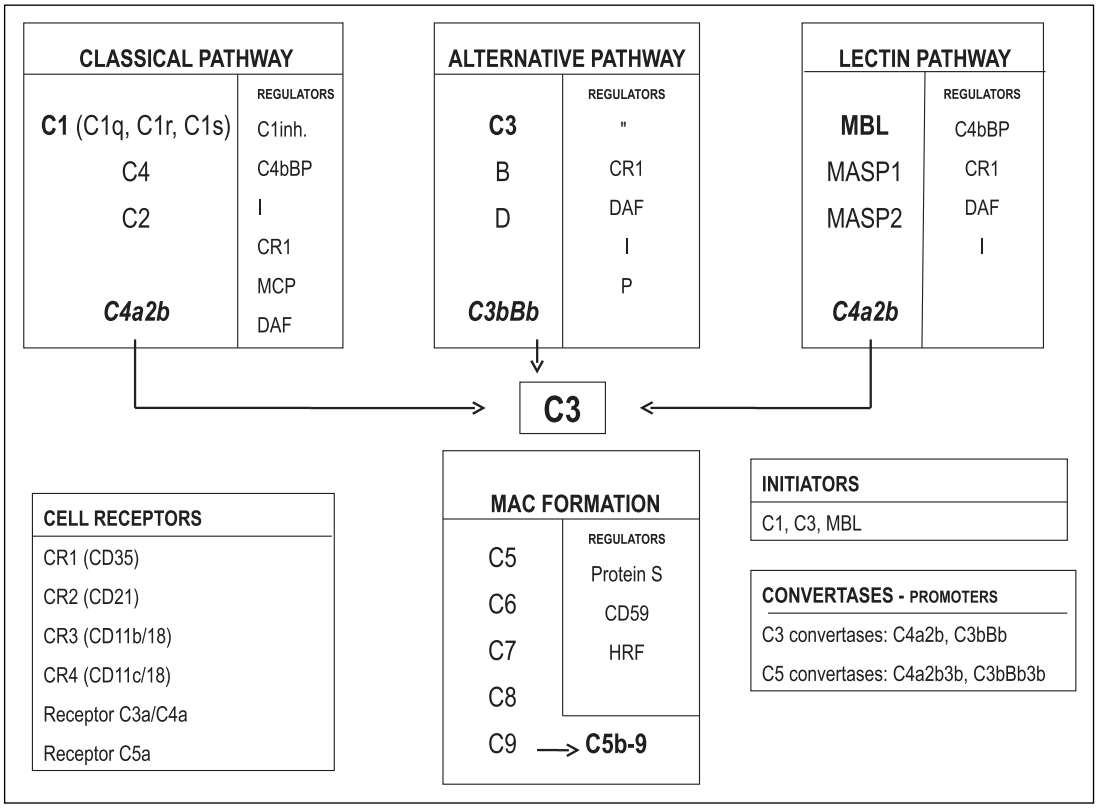

Figure 1. Classical, alternative, and lectin pathways.

Complement is activated in three ways: via the classical (immune complex–dependent), alternative (foreign surface–dependent), and lectin (mannan-dependent) pathways. All pathways unite at the level of the C3 component, forming C5 convertases, which initiate the formation of lytic complex (MAC or C5b-9). Activation products (C5a and C3a) have important biological properties because they are powerful chemo-attractants and anaphylatoxins.

The complement system significantly contributes to the development of autoimmune disease. If it acts without suppression, it destroys its targets ruthlessly and also damages the surrounding structures in the assaulted organs and tissues. Activation products such as C5a (anaphylatoxin) primarily attract neutrophils, but also other phagocytic cells, at the site of inflammation, further increasing the inflammation and thus aggravating the injury.

Localization of skin lesions

Complement-dependent dermatologic diseases may affect various distinctive skin layers. Bullous–blistering diseases such as pemphigus vulgaris are located in the intraepidermal stratum and are expressed by lesions resulting from lack of cohesion between individual epidermal cells; others are located in the subepidermal region and are characterized by deposition of immunoglobulin and C3 on the dermal-epidermal basement membrane (bullous pemphigoid) (17, 18). Lesions in dermatitis herpetiformis are also located in the sub-epidermal region and are associated with the involvement of diseases of the small intestine and Crohn's disease. Herpes gestationis is characterized by destruction of the basal-cell layer of the epidermis and deposition of C3, and factors P and B of the alternative pathway. In porphyrias, the dermal-epidermal junction is damaged. Lesions in urticaria and angioedema are localized in superficial parts of the dermis and subcutaneous tissue (19). Cutaneous vasculitis is characterized by inflammation of blood vessels in the skin (11). Signs of inflammation and the presence of neutrophils and other inflammatory cells are significant for all of these injury sites (18, 20).

Pemphigus vulgaris

The etiological cause of the disease is unknown. Infection with viruses is possible but treatment with some medications and some malignant diseases can also be accompanied by the eruption of blisters in the suprabasal region of the skin. Autoantibodies directed against desmosomes (e.g., desmosomal adhesion protein, desmoglein 1 [Dsg 1] and 3 [Dsg 3]) and protein BP180 are found in the lesions by direct immunofluorescence and are the major pathogenetic agent (21). These antibodies are thought to activate complement and cause acantholysis (22). Activation of complement has been demonstrated locally in blisters and systemically in blood by increased classical and alternative pathway activity (low CH50 and APH50), unchanged lectin pathway activity, and low concentrations of separate complement components, except for C8 and C9 (4, 23). There are also some other mechanisms involved in the pathogenesis of the disease. It has been reported that MIF is important in pemphigus vulgaris because it induces T cells and stimulates autoantibody production by B cells (24, 25).

Bullous pemphigoid

This disease is characterized by large, extended blisters in the subepidermal region of the skin. The pathogenetic agent is autoantibodies directed against antigens BP230, BP180, and desmoplakin, located in the basement membrane zone (25). Immune complexes composed of IgG together with C3 and C4 are found in histological preparations. The etiology of the disease is still unknown but it is more common in elderly persons with malignancies or consuming various drugs (26). Here, too, the antibodies are thought to activate the complement system. Serum and blister concentrations of all components of the complement cascade are lowered in laboratory tests, indicating complement activation (4, 7, 17, 27).

Herpes gestationis

This disease appears during or soon after pregnancy. Autoantibodies against collagen XVII are present in the majority of patients (28). Destruction of the basal layer of the epidermis and deposition of IgG, C3, FB, P, and C5b-9 are present in histology sections. There is hypocomplementenemia in the acute phase of the disease but not later. The presence of alternative pathway components in deposits suggests activation of both classical and alternative pathways (29, 30). The disease is associated with C4 null allele polymorphism (31).

Dermatitis herpetiformis

Dermatitis herpetiformis is characterized by small subepidermal blisters on an erythematous base with intense itching. Aside from pruritus, systemic involvement is rare (32). The disease is associated with gluten intolerance and small-intestine changes similar to Crohn's disease. Deposits of IgA together with C3, factor B, and factor P are found in histological resins. Because no C4 and C1 are present in depositions, it

has been suggested that local complement activation by the alternative pathway occurs preferentially (33).

Porphyria

Porphyrias are caused by a specific enzyme defect, and depositions of complement and immunoglobulin are present around the blood vessels at the dermal-epidermal junction (34). Activation of the complement system is also associated with accumulation of neutrophils and mast cells in the region of the skin lesions. Irradiation, which is often the triggering agent in porphyrias, may activate complement in vitro (35). This may be evidence that complement activation has a pathogenetic role in development of the disease.

Urticaria

In urticaria, edema predominantly involves the superficial parts of the dermis (36). The exact cause of the disease is unknown, but in several cases exposure to an allergen or physical stimulus has caused a skin reaction (37). The pathophysiological background of the reaction is in many cases degranulation of skin basophils due to the presence of IgE antibodies. Immune complexes in the skin are normally not found and direct involvement of the complement system is therefore not likely (38).

Angioedema (inherited C1 inhibitor deficiency)

The disease is very similar in appearance to urticaria but the pathologic events are located in the subcutaneous tissues and are directly connected with deficiency of the complement regulator C1 inhibitor (39). Hereditary angioedema is autosomally inherited (40). The incidence is about 1 in 150,000 and men and woman are equally affected. The disease is dominant and homozygous deficiency is not yet known. In 85% of cases, a low level of C1 inhibitor in plasma is found, and normal or elevated levels of functionally defective C1 inhibitor molecule are present in 15% of cases (41). Clinical symptoms are painless swelling of localized areas of skin, sometimes with the involvement of the gut and respiratory tract. Laryngeal swelling is life threatening. After an attack, C2 and C4 levels are substantially decreased. In some individuals, inherited C1 inhibitor deficiency is associated with immune complex diseases and profuse consumptions of the classical pathway components. An acquired form of angioedema also exists. The acquired form is common in patients with malignant lymphoproliferative disease of B cells. Low levels of C1q are usually present in such patients.

Urticaria and angioedema may also be a sign of systemic disease. Serum sickness and systemic lupus erythematosus often present with symptoms of hypersensitivity but are accompanied by abundant hypocomplementenemia.

Vasculitis

Vasculitis is characterized by inflammation of the blood vessels (10). The presence of immunoglobulin in the vessel walls is usually accompanied by complement component C3 and activation products of C3, C4, and C5b-9 complex. MAC is present on the surface of endothelial cells and infiltrating neutrophils and is apparently involved in cell damage and destruction via the Arthus reaction. Hypocomplementic urticarial vasculitis seems to be connected with systemic lupus erythematosus (42).

Complement deficiency states

Complement deficiency states are rare. All three pathways and terminal complex formation may be affected. Symptoms of skin disease are mostly present if the classical pathway is defective. Most patients have a similar clinical picture to systemic or discoid lupus erythematosus. The discoid form is mostly accompanied by C1q and C2 deficiency; the systemic form, however, by deficiency of C1q, C1r, C2, C4, and C3. Among complement deficiencies, a deficiency of C2 is prevalent (43). An SLE-like syndrome can also be seen in patients with factor H and factor I deficiency. Basal cell damage and immunoglobulin depositions are found in bioptic probes. Serum levels of complement are low in most patients with the systemic form of SLE but not in patients with the discoid form. Patients with profound hypocomplementemia may also present with SLE-related vasculitis. Biopsies of lesions show deposits of immunoglobulin, C3, and MAC at the dermal-epidermal junction. A deficiency of complement receptors may be involved in the pathology of SLE-like skin diseases. It has been found that patients with CR1 and CR2 deficiency frequently present with a picture of SLE (44). Complement deficiency has also been described for lichen planus, in which C4 component is deficient, and xeroderma pigmentosum, in which C8 deficiency is present (45, 46).

Systemic lupus erythematosus

The presence of various autoantibodies is significant for this disease, with anti-nuclear (ANA), anti-double stranded DNA, anti-Ro, and anti-La antibodies being present in most patients. These may be revealed with the use of the direct immunofluorescence tech-

Table 1. Complement in skin diseases: characteristics of immunohistological deposits and changes in serum concentration.

Disease	Location	Antigen	Autoantibodies/ cells	Deficiency of complement	Histology	Blood complement	Blister fluid
Pemphigus vulgaris	Dermal-epidermal junction, suprabasal region	Desmoglein (Dsg 1, Dsg 3), protein BP180	Anti desmosomal	Secondary, except C8 and C9	IgG, C1, C3, C4, FB, FH, P, C5b-9	Activation of classical and alternative pathway, unchanged lectin pathway, hypocomplementemia	Signs of complement activation
Bullous pemphigoid	Epidermal basement membrane	Protein BP180, BP230, desmoplakin	Anti-desmoplakin, anti-plektin	Secondary	IgG, C1, C3, C5, FB, P, C3d/dg, C5b-9	Secondary hypocomplementemia	Signs of complement activation
Herpes gestationis	Basal cell layer	Pregnancy, collagen XVII	Likely	Secondary, C4 null allele polymorphism	IgG, C3, FB, P, C5b-9	Hypocomplementemia in acute phase of disease	/
Dermatitis herpetiformis	Subepidermis		Likely	Gluten intolerance	IgA, C3, FB, P, C5b-9	Activation of alternative pathway	/
Porphyria	Dermal-epidermal junction, dermal blood vessels	Porphyrins	No Photoactivation, accumulation of neutrophils and mast cells	No	IgG, C3	Normal	/
Urticaria	Superficial dermis	Allergens, local physical trauma	IgE, basophils, eosinophils	No	Without immune complexes in the skin	Normal	/
Angioedema	Dermis and subcutaneous tissue	No	No	Inherited deficiency of C1 inh, secondary low C2 and C4	Immune complexes containing classical components of complement in some patients	Very low levels of C1 inh or normal or elevated levels with dysfunctional protein, secondary low C2 and C4	No blisters, swelling of localized areas of skin and laryngeal mucosa
Vasculitis	Blood vessels (venules) in dermis		Neutrophils; Arthus reaction	No	C3, C4, C5b-9 on endothelial cells	Hypocomplementemia common	/
Discoid lupus	Epidermis, basal membrane		Anti-nuclear (ANA) sometimes	Inherited or acquired deficiency of C1, C2, C3, and C4	Follicular hyperkeratosis	Hypocomplementemia rare	/
Systemic lupus erythematosus	Dermal-epidermal border	Double-stranded DNA, histones, Ro, La	Anti-nuclear (ANA), anti-double stranded DNA, anti-Ro (SS-A), anti-La (SS-B), and anticardiolipin antibodies	Inherited or acquired deficiency of C1, C2, C3, and C4, sometimes deficiency also of late components of the terminal pathway, involvement of CR1, C3bR, and Fc-gamma RIII	IgG, IgA, IgM immune complexes containing C1q and C3	Abundant hypocomplementemia common, extensive consumption of C3 and C4	Vacuolar and fibrinoid degeneration of epidermis, edema, inflammation of vessel walls
Partial lipodystrophy	Subcutaneous fat tissue	C3bBb	Autoantibody to C3bBb	Secondary deficiency of C3, presence of C3Nef		Low levels of C2, C3, and C4 are normal	/
Psoriasis	Transition between basal and horny layer, hyperkeratosis	Streptococcal and viral superantigens	No	Dysfunction of keratinocytes, dendritic cells, NK cells, T cells and neutrophils	C1, C3, C4	Activation of classical pathway	Activation of immune system with production of inflammatory cytokines
Complement deficiency	Basal cell damage, similar to systemic or discoid lupus	No	No	C1q, C1r, C3, C4, in most cases C2, sometimes FH and I, deficiency of CR2 and CR2	In acquired deficiency immunoglobulin deposits, C3 and C5b-9	Absence or low levels of deficient component or dysfunctional component	/
Xeroderma pigmentosum	Hyperkeratosis, papillomatosis, skin atrophy	No	No	Autosomal inherited defect of endonucleases, C8 defect	/	Defect of C5b-9 formation if there is a C8 defect present	/

nique in histological preparations. The involvement of complement in the pathogenesis is evident from the presence of C1q and C3 joined with IgG, IgA, and IgM in immune complexes along the dermal-epidermal border. Abundant activation of the classical pathway of the complement is frequently present in the serum, indicated by very low concentrations of total hemolytic complement, with or without evidence of deficiency of C1q, C2, C4, and sometimes terminal complement components (47–51). Concentrations of C3 and C4 in serum are lowered, too, at times of exacerbation, because of their extensive consumption (52). Measurement of the concentration of complement component split products such as C3d and C4d may have diagnostic value (53, 54). Recently, the involvement of several complement receptors, such as CR1, C3b receptor, and Fc-gamaRIII, has been reported in the pathogenesis of the disease (55).

Discoid lupus

Congenital or acquired deficiencies of classical pathway components C1, C2, C3, and C4 are very often present with this disease. The disease is closely related to SLE but systemic symptoms are mild or absent. Lesions are discoid, erythematous, scaling and chronic, and sensitive to sunlight.

Partial lipodystrophy (Barraquer-Simons syndrome)

The disease is characterized by an unusual distribution of subcutaneous fat. Patients are born with normal fat distribution but in early puberty fat in the extremities and, in some cases, also in the trunk, disappears locally (56). This is followed by increased fat in the face and neck after puberty is completed. Visceral fat and intramuscular fat deposits are preserved. In patients with partial lipodystrophy there is sometimes an association with renal disease (57). Secondary deficiency of C3 is significant for this disease. Lack of C3 is caused by the presence of C3NeF, autoantibody to C3bBb, a convertase of the alternative pathway. C3NeF stabilizes this convertase, causing abnormal complement activation. Levels of serum C3 are low, with normal C2 and C4 indicating activation of the alternative pathway.

Psoriasis

Psoriasis is one of the most frequent skin diseases in Europe and North America. The etiology of the disease is still mysterious. It is a multifactorial disease with elements of inheritance, dysfunction of the endocrine system, and activation of the immune response (16, 58, 59). The keratinocyte biology is important for some manifestations of psoriasis. Keratinocytes are producers of several complement components, such as C3, factor B, factor H, and factor I (60). They release C7 and C9. They are also a source of several cytokines, which are important for the synthesis of complement proteins and regulation of their release. It has recently been found that TNF alpha increases C9 synthesis and thus contributes to the formation of membrane attack complex (61). The involvement of cellular immunity also seems to be very important. Dendritic cells, T cells, NK cells, and neutrophils contribute to the development of psoriatic lesions. Activity of the neutrophils is increased by complement split products and they release inflammatory molecules at the site of activation, aggravating the cellular response.

Recurrent cutaneous infections

Recurrent cutaneous infections are rare in complement deficiency. Deficiency of factor I and CR3 have been described as being connected with cutaneous infection (14, 62). Secondary complement deficiency more often presents with infected skin lesions (63).

Diagnostic procedures in determining the involvement of complement in a disease

Diagnosis of complement involvement in the pathogenesis of disease is performed by analysis of histopathological changes in the skin, serum, or plasma (5). Diagnosis follows the principle of gradual investigation of complement cascade activation and formation of lytic complexes (64). Biological determination of destruction of the target cells (erythrocytes) is still the basis of the diagnostic protocol. If cells have been destroyed to a major or minor extent in comparison to normal control, the system has been activated. If there is almost no destruction *in vitro*, the system is either over-activated or defective. Demonstration of split products of central components such as C3, C4, and C5 now leads to consideration of whether complement is really activated. If complement is activated, components are cleaved and therefore consumed, there will be no formation of lytic complex, and the split products (e.g., C3a, C3d/dg, C4d, and C5a) are present in high concentrations. If there is a defect of some component in the cascade, or if it is non-functional, concentration of split products is normal or low. Because there is a discontinuance in the cascade, the lytic complex is not formed, and in vitro we anticipate zero activity of the complement system (15).

We usually use the following tests for complement testing: the CH50 test (activation of the complement system by the classical pathway, by 50% activity), APH50 (activation of the complement system by the alternative pathway, by 50% activity), the activation of the mannan pathway with determination of MBL (mannan-binding lectin) concentration, or with demonstration of C5b-9 complex after mannan activation of the serum with the ELISA test. Concentration of the single components of the complement cascade is achieved by the classical RID (radial immune diffusion method) or nephelometrically. The concentrations of split products are determined by specific ELISAs. The activity of C1 inhibitor is demonstrated by the colorimetric test.

If biological activity of the complement (CH50 or APH50 or both) is low or very low, defective function of some of the components may be suspected. In such a case, the presence and function of individual complement components should be tested, but this is cumbersome and requires extensive experience.

However, the involvement of complement in the pathogenesis of skin diseases can be investigated effectively if it is believed that such an approach will be of benefit for the patient. Currently, trials to discover therapeutic possibilities of treating complement-dependent disorders in skin diseases are underway (65–69). Small inhibitory molecules should interfere with split products of complement components such as C5a and inhibit their pathological effectiveness, suppressing inflammation and the secondary involvement of neutrophils in the development of lesions (69, 70). Targeting the complement system is an attractive therapeutic possibility. Specific inhibition of complement activation may block proinflammatory pathways and mediate effector responses in autoimmune, infectious, cardiac, and allergic diseases (71).

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