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Review

Current insights in the pathogenesis of scleritis

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ABSTRACT

Scleritis is a sight-threatening inflammation characterized by severe pain and redness of the eye. It can cause blindness by severe complications like scleral and corneal necrosis, keratitis, and uveitis. The pathogenesis of scleritis is largely unknown due to a combination of the rarity of the disease, the little available human tissue-based research material, and the lack of animal models. The immune system is assumed to play a crucial role in the pathogenesis of scleritis. Multiple clues indicate probable antigenic stimuli in scleritis, and the involvement of matrix metalloproteinases in the destruction of scleral tissue. In this article we review the current insights into the pathogenesis of scleritis, and we suggest new hypotheses by implementing knowledge of systemic autoimmune disease pathogenesis. Understanding the pathogenesis of scleritis is crucial to improve the clinical management, as well as to find novel treatment modalities.

1. Introduction

Scleritis is an uncommon inflammation of the outer coat of the eye referred to as sclera. The inflammation is generally characterized by intense pain of the affected eye, and in severe cases may lead to visual loss or even blindness (Watson and Hayreh, 1976; Wieringa et al., 2013). Although scleritis is considered to be relatively rare, exact numbers on incidence and prevalence are lacking (Okhravi et al., 2005; Sainz de la Maza et al., 2012a). A crude estimate of the incidence rate of scleritis is 4 per 100.000 person years. Scleritis occurs more often in females than in males, and commonly affects the middle-aged population (Homayounfar et al., 2013). Causes of scleritis are varied with up to 50% of cases being associated with systemic autoimmune diseases, including rheumatoid arthritis, ANCA-associated granulomatosis with polyangiitis (GPA), and relapsing polychondritis. (Sainz de la Maza et al., 2012b; Watson and Hayreh, 1976). Less frequent, scleritis is caused by local or systemic infection, trauma, specific drugs, irradiation, or malignancy. This review focusses on idiopathic and immune mediated scleritis. The exact clinical impact is not precisely known, but is presumably very high. Scleritis can become resistant to various treatment modalities, resulting in untreatable pain, and severe ocular complications. In rare cases, scleritis may ultimately require enucleation. As a consequence, scleritis can significantly affect a patient's quality of life (Akintayo et al., 2019; Sharma et al., 2019).

The classification of scleritis by *Watson and Hayre* from 1976 is still being used. This classifies scleritis cases into anterior or posterior, and further into diffuse, nodular, or necrotizing scleritis based on clinical findings (Watson and Hayreh, 1976). The clinical presentation of scleritis, its systemic manifestations and outcomes have been well described (Abd El Latif et al., 2018; Ando et al., 2019; Lane et al., 2018; Sainz de la Maza et al., 2012b; Tanaka et al., 2018; Watson Peter G and Jaypee, 2012; Wieringa et al., 2013; Yang et al., 2018). In contrast, the pathogenesis of scleritis represents an underexposed area of interest. Possible reasons include the relative rarity of the disease, the lack of animal models, and scarcity of available human tissue-based research material.

A crucial role of the immune system in the pathogenesis of scleritis is very likely. Several hypotheses have been proposed, including both cell-mediated and humoral, antibody-mediated, mechanisms. New insights in the pathogenesis of systemic autoimmune diseases, that are associated with the development of scleritis, may be beneficial to further elucidate that of scleritis (Wakefield et al., 2013b; Watson and Romano, 2014; Watson and Young, 2004). At present though, the pathogenesis of this potentially blinding disorder is poorly understood. An increased insight in the pathogenesis of scleritis is expected to improve clinical outcome and enrich the potential for novel treatment

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Abbreviations

ACPA	Anti-citrullinated-protein antibody
ANA	Antinuclear antibodies
Anti-CCP	Anti-cyclic citrullinaded peptide
Anti-MCV	Anti-mutated citrullinated vimentin
cANCA	Anti-neutrophil cytoplasmic antibody, cytoplasmic
CTLA4	Cytotoxic T lymphocyte-associated antigen-4
FAG	Fluorescein angiography
GPA	Granulomatosis with polyangiitis
HLA	Human leucocyte antigen
ICG	Indocyanine green angiography
IFN-γ	Interferon gamma
MHC	Major histocompatibility complex
MMP	Matrix metallo proteinase
OCT	Optical coherence tomography
pANCA	Anti-neutrophil cytoplasmic antibody, perinuclear
PG	Proteoglycans
PTPN22	Protein tyrosine phosphatase non-receptor type 22
SLE	Systemic lupus erythematosus
SNP	Single nucleotide polymorphism
TIMP	Tissue inhibitor of matrix metalloproteinase
UBM	Ultrasound biomicroscopy

modalities.

In this article we will review the current insights in scleritis with emphasis on its pathogenesis, and we will discuss relevant current and potential future lines of research on scleritis.

2. The anatomy and components of the sclera

Sclera derives from the Greek word “σκληρος” meaning “hard”, and comprises five-sixth of the eye's surface. The average thickness is approximately 0.7 mm, which increases near the optic nerve, and decreases towards the recti muscles. The sclera is continuous with Tenon's capsule. This capsule encloses the recti muscles, and forms a muscle pulley for the extraocular muscles. Underneath Tenon's capsule is the episclera, a thin and densely-vascularized layer of connective tissue. The innermost layer of the sclera blends into the choroidal stroma and is called the lamina fusca. The nourishment of the scleral stroma is provided by the choroidal and episcleral vasculature. The choroidal vascular network consists of anastomoses of superficial and deep choroidal end arteries, which causes a sluggish or oscillating blood flow (Meyer, 1988; Watson and Romano, 2014). The episcleral vascular network derives its blood supply from the anterior- and posterior ciliary artery (Watson and Young, 2004). Blood vessels and nerves transverse the scleral stroma through perforating canals or emissaria. No capillary network is present in the sclera. The nerve supply of the sclera is rich, and consists of short- and long ciliary nerves (Wakefield et al., 2013b; Watson and Young, 2004).

The scleral stroma obtains its resilience and strength from bundles of irregular-aligned collagen fibrils grouped into dense lamellae. This arrangement, in contrast to the parallel-aligned collagen fibrils in the cornea, determines the sclera's non-transparency. Elastic fibers, fibroblasts, few macrophages, and dendritic cells intermingle with the collagen fibers. The scleral stroma consists mainly of collagen type I. Thereby, small amounts of collagen type II-XV, XVIII and XIX are present (Watson and Young, 2004; Young et al., 2004). Elastic fibers represent approximately 2% of the human sclera, and are located predominantly in the lamina fusca. In the extracellular matrix of the scleral stroma, proteoglycans (PG) have been identified (Coster and Fransson, 1981; Wakefield et al., 2013b; Watson and Young, 2004). Mainly decorin, biglycan and small amounts of the large PG aggrecan (similar to the well-known cartilage aggrecan) were reported (Ward et al., 1987). The PGs encircle and connect collagen fibers (Watson and Romano, 2014). Especially decorin has been proven to be crucial in adhesion of collagen, as the reduction of decorin was found to be associated with development of myopia in marmosets (Watson and Romano, 2014). Fibroblasts are crucial to maintain the scleral structure (Wakefield et al., 2013b). Many similarities between scleral and cartilage tissue have been reported. Despite the fact that sclera is mainly characterized by collagen type I, and cartilage consists mainly of collagen type II (Orr et al., 2017).

3. Genetic predisposition

3.1. HLA-association

Various ocular inflammatory disorders are associated with specific human leucocyte antigen (HLA) alleles. (Goverdhan et al., 2005). The HLA gene complex, located at chromosome 6, encodes HLA class I (A, B and C) and HLA class II (DR, DP and DQ) molecules. The most prominent function of the HLA complex is the presentation of peptide antigens to T-cells (Goverdhan et al., 2005). Association between HLA alleles and disease indicates the involvement of (auto)immune mechanisms in disease pathogenesis. So far, besides a possible association with HLA-B27 found in five patients, no genetic predisposition based on HLA association has been identified in scleritis (Anshu and Chee, 2007; Okhravi et al., 2005; Watson and Young, 2004). Rheumatoid arthritis, in contrast, often observed in combination with scleritis, is clearly associated with an allele of HLA-DR4 and HLA-DR1, as well as with alleles of HLA-DR13 and HLA-DR15 (Karami et al., 2019). The HLA-DR4 allele was also found to be associated with relapsing polychondritis (Terao et al., 2016), while the HLA-DR15 allele was also found to be associated with systemic lupus erythematosus (SLE) and ANCA-associated vasculitis (Javinani et al., 2019; Rahmattulla et al., 2016). In SLE, besides HLA-DR15, other alleles of HLA-DR were found to more prevalent. Thereby, a gene polymorphism in HLA-DP, which was also found in rheumatoid arthritis, was implicated to be associated with SLE (Huang et al., 2018; Javinani et al., 2019). Interestingly, the HLA-DR15 allele was found to be a possible predisposing factor for corneal ulceration in response to inflammation, however this was not typical for scleritis (Watson and Young, 2004).

3.2. Non HLA-association

A single study investigated non-HLA gene susceptibility loci in a large cohort of 432 patients with non-infectious scleritis. The authors focused on two genes, the cytotoxic T lymphocyte-associated antigen-4 (*CTLA4*) and the protein tyrosine phosphatase non-receptor type 22 (*PTPN22*). Both genes regulate the control of T-cell activity, and polymorphisms were previously reported to be involved in the development of autoimmune responses. A *CTLA4* single nucleotide polymorphism (SNP) was found to be a predisposing factor for posterior scleritis, and a risk association of a specific *PTPN22* haplotype and scleritis was found in this large cohort (Li et al., 2019). PTPN22 and CTLA4 were also reported as susceptibility loci in rheumatoid arthritis. Genome wide association studies were repeatedly performed in rheumatoid arthritis, in which additional SNPs in genes were discovered, including *TRAF1, STAT4, IRF5, CCR6, IL23R and PAD14* (Karami et al., 2019). Some of the previously mentioned gene loci were also associated with GPA and SLE (Deng and Tsao, 2017; Relle et al., 2016). The majority of associated gene loci were implicated to be involved in antigen presentation and B-cell function (Karami et al., 2019). The relevance of these genes in the pathogenesis of scleritis is unknown.

4. Histo- & immunopathology in scleritis

Histopathological examinations of scleral tissue from patients with scleritis are scarce. Biopsies in scleritis are often contraindicated, as any kind of surgery may induce or aggravate scleral inflammation. A majority of the limited information arises from advanced scleritis cases, specifically from enucleated eyes during the end stage of the disease. Thereby, the available findings demonstrate a large heterogeneity.

4.1. Subtypes

Based on histopathological findings, several subtypes of scleritis can be distinguished. In scleritis associated with systemic autoimmune diseases, the necrotic scleral areas are accompanied by zonal granulomatous inflammation with polymorpho-nuclear granulocytes and macrophages. The necrotic areas are predominantly surrounded by $CD20^+$ B-cells and CD138+ plasma cells, and are sometimes accompanied by vasculitis. Scleritis without an associated systemic disorder showed a non-specific chronic leucocyte infiltration without necrosis, characterized by $CD3^+$ T-cells, plasma cells and occasional B-lymphoid follicles with few macrophages, and polymorpho-nuclear granulocytes (Rao et al., 1985; Riono et al., 1999; Usui et al., 2008). Considerable overlap between these proposed groups on histopathological findings was noted (Hankins and Margo, 2019). Interestingly, a recent study showed that probable or definite IgG4 related disease could be observed in five of fifteen idiopathic scleritis cases. Providing a possible subtype in the group of idiopathic scleritis patients (Karim et al., 2017a).

4.2. Immune complexes

Accumulation of immune complexes of IgM and IgG type was repeatedly described, however their origin and exact role are unknown (De la Maza and Foster, 1991; Díaz-Valle et al., 1998; Hembry et al., 1979; Lye Pheng et al., 1991; McCluskey et al., 1985; Wakefield et al., 2013a). The deposition of immune complexes can exaggerate inflammatory microangiopathy, in which the complement system seems likely to be involved. C1q was particularly found in the anterior sclera of healthy donors, while other complement factors were present in the whole sclera (Brawman-Mintzer et al., 1988, 1989). Inflammatory microangiopathy may contribute to the initiation and maintenance of scleral inflammation and damage. The damaged sites of the vascular endothelium were noted to express HLA-DR, which is a HLA class II cell surface receptor (Díaz-Valle et al., 1998; Hankins and Margo, 2019; Watson and Young, 2004). The expression of class II HLA antigens is not expected in healthy scleral tissue, as normally only professional antigen presenting cells express HLA class II. A similar finding was found in inflamed joints of patients with rheumatoid arthritis, where fibroblasts expressed high levels of HLA-DR antigens. The expression of the HLA class II in these tissues may hypothetically be induced by inflammatory cytokines (Goverdhan et al., 2005).

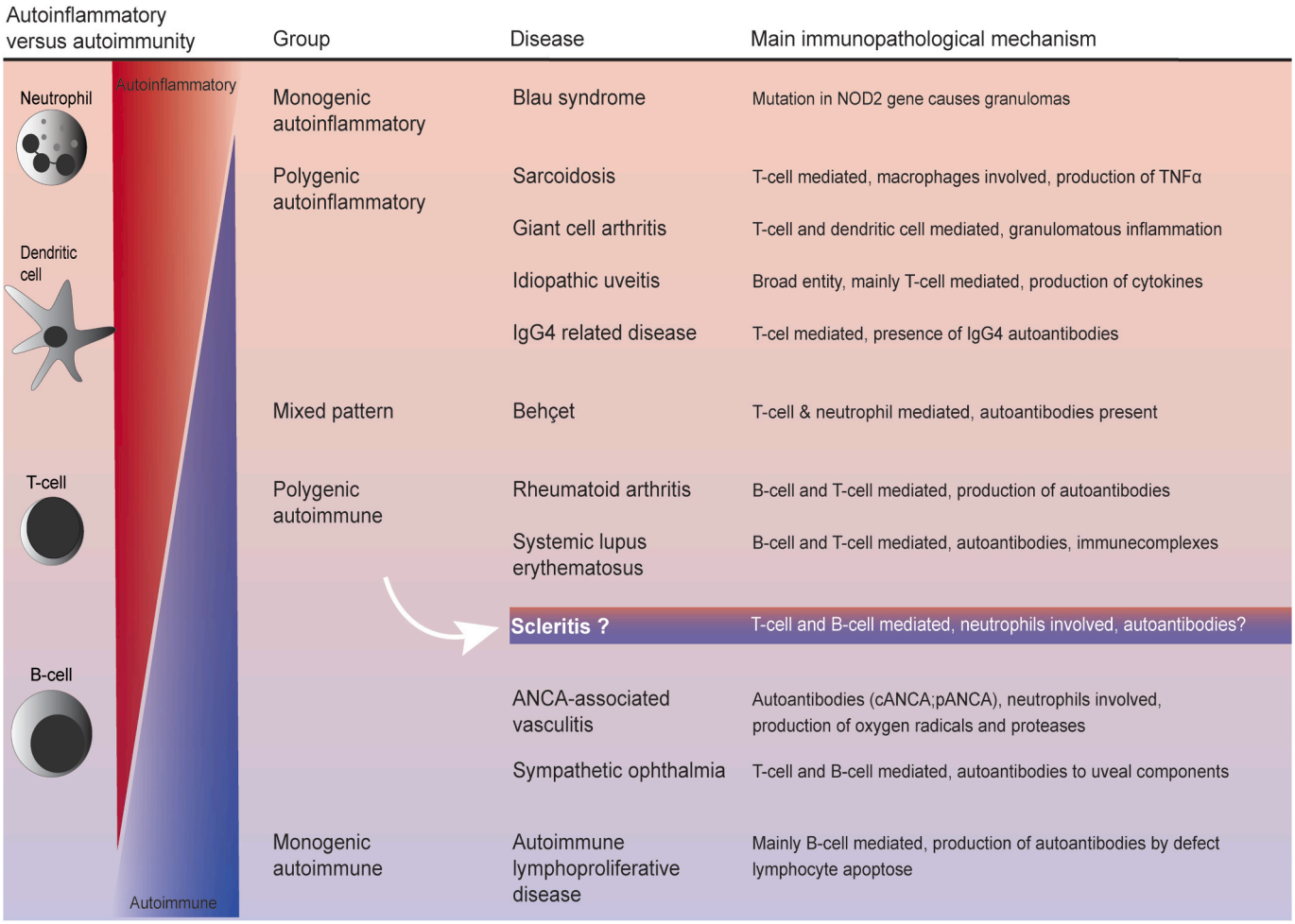

Fig. 1. Overview of the main immunopathological mechanisms of several autoimmune versus autoinflammatory ocular- and systemic diseases. At present it is unclear where scleritis is situated in this overview. Arguments for scleritis to be autoimmune mediated are present. However, specific autoantibodies or self-antigens are hardly elucidated. Relapsing polychondritis also remains to be classified. In this image, based on the image of McGonagle et al., the list of diseases is obviously not complete (McGonagle and McDermott, 2006).

4.3. Additional findings

Elevated expression of adhesion molecules (CD11a/18: lymphocyte function associated antigen 1, LFA-1, and CD54: intercellular adhesion molecule 1, ICAM-1) was described. These adhesion molecules could enhance the infiltration of lymphocytes, and may contribute to the ongoing inflammation. Fas (CD95) and FasL (CD95L), specific markers for apoptosis, were abundantly present in biopsies of necrotizing scleritis. Increased apoptosis of T-cells could indicate local activation of T-cells. However, it is not yet known which cells show increased markers for apoptosis (Díaz-Valle et al., 1998; Levy-Clarke et al., 2009; Wakefield et al., 2013a).

4.4. Necrosis

Two possible explanations for the extensive necrosis that occurs in some scleritis cases have been noted. At first, necrosis can be a result of ischemia. Ischemia is either caused by occlusive vasculitis, or by insufficient vascular flow resulting from inflammation in a preexistent low vascularized tissue. Secondly, necrosis can be a result of the breakdown of collagen fibrils and its surrounding proteoglycan matrix by proteolytic enzymes. Histopathological images of necrotic sclera show swelling and unraveling of collagen fibrils, as well as an increased distance between the fibrils. Subtle changes were observed in areas around necrosis, consisting of activated fibroblasts. This supports the explanation that destruction of the scleral matrix, by proteolytic enzymes, precedes the development of necrosis (Sevel, 1968; Watson and Young, 2004; Young et al., 1988; Young and Watson, 1984a, b).

5. Autoimmunity in scleritis

The hypothesis of an autoimmune origin of scleritis was already proposed in the early 80s by *Wilhelmus* et al., and has been repeatedly suggested (Aragaki et al., 2007; James et al., 1985; Wakefield et al., 2013a, b; Watson and Young, 2004).

5.1. Autoimmunity versus autoinflammatory

Autoimmune diseases are characterized by the production of specific autoantibodies and/or the presence of auto-reactive T-cells. The primarily involved immunological mechanisms belong to the adaptive immune system (McGonagle and McDermott, 2006). The pathogenic role of the involved autoantibodies is often unknown. For example antinuclear antibodies (ANA), present in SLE, are also present in healthy subjects (Marin et al., 2009). In autoinflammatory diseases, such as Behçet's disease, Crohn disease or sarcoïdosis, a self-directed inflammation of predominantly the innate immune system occurs (McGonagle and McDermott, 2006; ten Berge et al., 2018). The majority of scleritis cases is associated with autoimmune diseases, while a minority is associated with previously mentioned autoinflammatory diseases. However, it is unknown so far if the innate or the adaptive immune system plays a predominant role in idiopathic scleritis (Fig. 1). (Akpek et al., 2004; Watson and Hayreh, 1976)

5.2. Autoantibodies

In idiopathic scleritis, the presence of antibodies directed against two sclera-specific antigens was noted only once. The antigens had a molecular weight of 15 kDa and 45 kDa (Aragaki et al., 2007). This study was conducted in two patients and the presence of auto-antibodies is not yet confirmed in a larger cohort (Wakefield et al., 2013b). Specific autoantibodies are clearly involved in the pathogenesis of some of the systemic autoimmune diseases associated with scleritis, such as GPA, SLE and rheumatoid arthritis. In GPA, the anti-neutrophil cytoplasmic autoantibodies (mostly cANCA: an antibody against proteinase 3, and sometimes pANCA, an antibody against myeloperoxidase) are prominently involved in the development of vasculitis. In SLE, anti-dsDNA antibodies are clearly associated with renal pathology (lupus nephritis). In rheumatoid arthritis, rheumatoid factor and antibodies against collagen, fibronectin, keratin and especially citrullinated protein (ACPA, including anti-CCP and anti-MCV) have been found, in which the latter is predictive for more severe joint damage. (Margo and Harman, 2016).

5.3. Candidate antigens

Knowledge of the pathogenesis of the aforementioned systemic diseases might help to clarify that of scleritis, because of resemblances. For example, collagen and the extracellular matrix proteoglycans are commonly found in both joint, tissue involved in rheumatoid arthritis, and sclera (Orr et al., 2017; Watson and Young, 2004). Human scleral cells share common characteristics with chondrocytes in joints, such as the potential to produce collagen type II when stimulated with specific cytokines (Seko et al., 2008). In addition, histopathological findings disclose resemblances between synovitis and scleritis (Orr et al., 2017; Wakefield et al., 2013b; Watson and Young, 2004; Young et al., 1988; Zierhut et al., 1994). Interestingly, high levels of anti-collagen type II antibodies were found in synovial fluid of patients with rheumatoid arthritis and were even suggested to initiate arthritis (Nandakumar, 2010; Rowley et al., 2008). Anti-collagen type II antibodies were likewise found in relapsing polychondritis (Lekpa and Chevalier, 2018; Sainz-De-La-Maza et al., 2016). Candidate antigens in scleritis thus may include collagens, proteoglycans, and other extracellular matrix proteins, which are abundantly present in scleral tissue (Young et al., 2004). Another possibility is the occurrence of novel antigenic epitopes in damaged scleral tissue.

The process that initiates the autoimmune cascade in scleritis, as well as in systemic disorders, is so far not known. In addition to genetic and immunological factors, environmental factors were suggested to be involved, including trauma and bacterial or viral infections (Wakefield et al., 2013b; Watson and Young, 2004). In several autoimmune diseases, molecular mimicry is suggested to facilitate autoimmunity. In this situation, autoreactive T-cells and/or autoantibodies are expanded as a result of stimulation by an exogenous molecule with cross-reactive epitopes to that of a self-antigen (Cusick et al., 2012). The cross reactivity of C. Jejuni and motor neuron axons in Guillain Barré syndrome is well-known. Also in rheumatoid arthritis and SLE cross reactivity of microorganisms and human proteins have been found to be involved in the pathogenesis (Rojas et al., 2018). This explanation is not exclusive, and the role of molecular mimicry in scleritis has not yet been proven.

6. Animal studies

The restricted knowledge on the pathogenesis of scleritis is partly due to the limited number of animal studies available. To the best of our knowledge, there are three successful laboratory animal models on scleritis and only a few histopathological studies on scleritis in dogs.

6.1. Histopathological evaluations in animals

Histopathological findings in dogs are comparable to the histopathological studies of affected scleral tissue in humans. Enucleated eyes of dogs affected by scleritis were characterized by granulomatous inflammation, macrophages expressing class-II HLA, $CD3^+$ T-cells and IgG positive plasma cells. Perivascular depositions of IgG-antibodies were found in some cases (Day et al., 2008; Grahn and Sandmeyer, 2008). Additionally, *Denk* et al. showed an altered staining pattern with Masson's trichrome stain of damaged collagen in scleritis tissue. This has also been observed in animals affected by a collagen disorder, and indicates damage of collagen fibers. The majority of dog breeds described in histopathological evaluations of scleritis have a genetic predisposition to autoimmune diseases (e.g. the English Cocker Spaniel). (Kennedy et al., 2006).

6.2. Animal models

The first experimental animal model for scleritis consisted of ovalbumin sensitized rabbits, and described the development of scleral and adjacent corneal inflammation after injection of ovalbumin into the limbus. The experiment was performed to describe clinical progression, and the histopathology of the scleral infiltrate (Hembry et al., 1979). A murine model for human autoimmune diseases (MRL/Mp-lpr/lpr mice) reported the development of scleritis at older age in multiple mice (Jabs et al., 1985). The lpr/lpr phenotype results from an autosomal regressive mutation in the Fas (CD95) gene causing massive benign lymphadenopathy. This is seen in autoimmune lymphoproliferative disease as well, providing an argument for autoimmunity in scleritis. These MRL/Mp-lpr/lpr mice also showed increased Il-1β and MMP-1 concentration at the cornea due to their genetic basis (Okamoto et al., 2004). Finally, another murine model of anterior scleritis was established by modifying a collagen-induced autoimmune arthritis model. Mice were sensitized with collagen type II, and consequently developed anterior scleritis with features of an immune complex deposition disorder (Taniguchi et al., 2015). The presence of collagen type II in scleral tissue, although minimal, may indicate an antigen specific immune reaction.

7. Role of matrix metalloproteinases

Scleral necrosis or scleromalacia is the most severe complication of scleritis (Fig. 2). The prevalence of necrosis of scleral and/or peripheral corneal tissue in scleritis varies from 6 to 28%. Matrix metalloproteinases (MMPs) probably play a crucial role in the development of necrosis, similarly to tissue destruction elsewhere in the body (Di Girolamo et al., 1997; Wakefield et al., 2013b; Watson and Young, 2004).

The human body contains multiple functional proteolytic enzymes (including MMPs), which are capable of degrading (extracellular) matrix proteins (Rose and Kooyman, 2016). MMPs represent a family of enzymes capable of degrading collagen. Physiologically MMPs are effective mediators of tissue remodeling, wound healing and embryologic development (Wakefield et al., 2013b; Watson and Hayreh). Disbalance in the level of MMPs and their inhibitors, the tissue inhibitors of matrix metalloproteinase (TIMPs) may lead to extensive degradation of collagen (Wakefield et al., 2013b). For example, in cancer MMPs are needed for tumor progression and play a role in development of metastases (Gonzalez-Avila et al., 2019).

7.1. Evidence of MMPs in scleritis

A disbalance of MMPs and their inhibitors is suggested to occur in scleritis. The level of the pro-inflammatory cytokine TNFα in tear fluid was found to be increased in patients with necrotizing scleritis. TNFα is a potent inducer of MMP production by scleral fibroblast (Fig. 3) (Seo et al., 2006). In addition, TIMP-1, the natural inhibitor of MMPs, was found to be less expressed in diseased scleral tissue (Di Girolamo et al., 1998). In the scarce reports on scleritis, specifically MMP-3 and -9 were found to be increased in scleral tissue and tears of patients with necrotizing scleritis (Fig. 3) (Di Girolamo et al., 1997; Seo et al., 2006; Young et al., 2004). This excess of MMPs could induce collagen degradation, which is seen by unraveling of collagen in histopathological images. Nevertheless, the exact pathophysiological process of scleral necrosis is not yet clarified.

7.2. Research in rheumatoid arthritis

In contrast to the scarce reports on scleritis, extensive research on MMPs in the destruction of cartilage has been performed in rheumatoid arthritis. Collagen in cartilage tissue is degraded by the actions of MMP-1, -8, -9, -13 and −14, whereof MMP-1 and MMP-13 were believed to be most important in cleaving collagen type II. Collagen type I, which is the main component of sclera, is most actively destroyed by MMP-8 in rheumatoid arthritis (Burrage et al., 2006). MMP-14 was proposed to regulate the destruction of collagen, and to control fibroblast-induced angiogenesis in inflamed joints (MacNaul et al., 1990; Sabeh et al., 2010; Wakefield et al., 2013a). Further, *A disintegrin and metalloproteinase with thrombospondin motifs* (ADAMTS), a more recently discovered member of the MMPs, is also involved in the destruction of cartilage in rheumatoid arthritis. The ADAMTS not only degrade collagen, but also degrade the PG aggrecan (ADAMTS-1, -4, -5, -8, -9 and -15) (Burrage et al., 2006). Finally, non-collagen matrix proteins in rheumatoid arthritis may also be degraded by the stromelysins (MMP-3, -10 and −11) (Burrage et al., 2006; Rose and Kooyman, 2016). Aggrecan and other matrix molecules are also found in scleral tissue and in consequence represent potential targets for these proteases in scleritis.

8. Biomarkers in scleritis

A biomarker is defined as a substance, structure or a process, that either influences or predicts incidence and/or outcome of disease. A biomarker needs to be objective and quantifiable (Strimbu and Tavel, 2010). Considering scleritis, previous research has focused on biomarkers predicting the development of systemic autoimmune diseases in patients with scleritis. Research focusing on biomarkers predicting the development, severity and/or prognosis of scleritis remains very limited.

8.1. Possible biomarkers for diagnosis of systemic diseases in scleritis

Systemic autoimmune diseases are more prevalent in patients with scleritis, compared to the general population (Wieringa et al., 2013). The systemic autoimmune disease manifests either prior to, or after the onset of scleritis. Useful screening markers to diagnose systemic autoimmune diseases are cANCA an pANCA for systemic vasculitis, RF and ACPA (mostly anti-CCP) for rheumatoid arthritis, and ANA and anti-dsDNA for SLE (Akpek et al., 2004; Lin et al., 2008; Mills et al., 1991; Orr et al., 2017; Wakefield et al., 2013b). Furthermore, increased serum IgG4 can indicate IgG4 related disease, belonging to the systemic autoinflammatory diseases (Karim et al., 2017b). However, in a great percentage of patients with scleritis no cause can be established. In addition, predicting scleritis in patients with systemic diseases, is not yet possible.

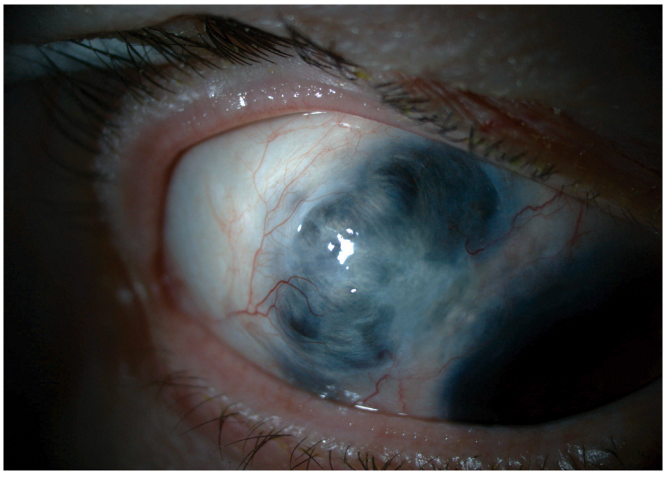

Fig. 2. A 72-year old patient with granulomatosis with polyangiitis (GPA) developed severe scleral thinning following strabismus surgery.

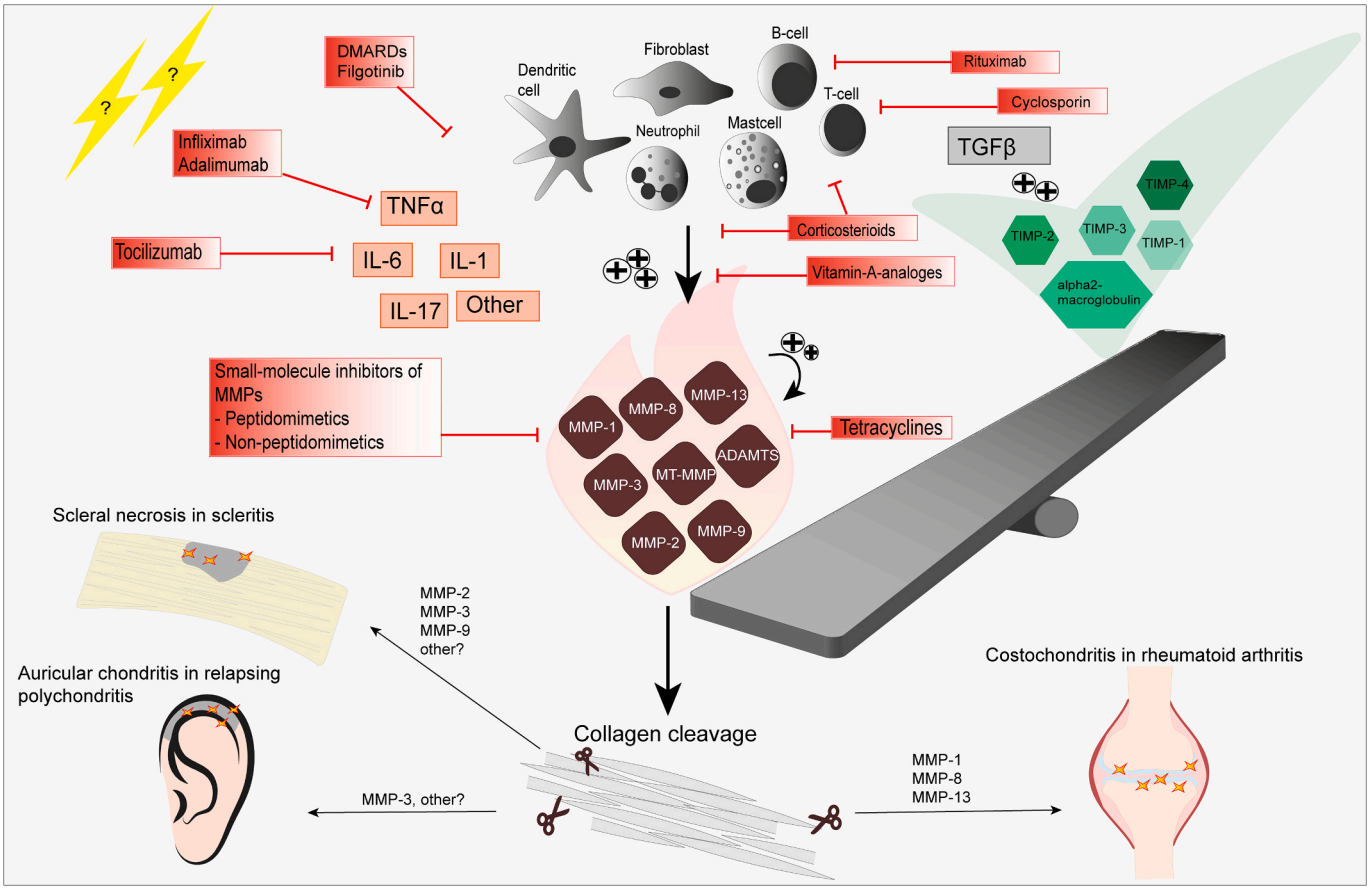

Fig. 3. Overview of the destructive potential of matrix metalloproteinases (MMPs).
An undifferentiated stimulus may lead to the production of pro-inflammatory cytokines. These cytokines (including IL-1, TNFα, IL-6 and IL-17) can activate the production of MMPs by fibroblasts and other immunologic cells. When the level of MMPs, MT-MMPs and ADAMTS rises, the balance between MMPs and their inhibitors can be disturbed. An excess of MMPs can lead to degradation of collagenous tissue in scleritis, as well as in relapsing polychondritis, and in rheumatoid arthritis. Inhibition of MMPs may be provided in several ways. At first, inhibition of pro-inflammatory cytokines, and immunological cells. Secondly, direct inhibition of MMPs, and finally, the inhibition of signal transduction pathways.DMARDs: Disease modifying anti-rheumatic drugs; IL-1: interleukine-1; IL-6: interleukine-6; TNFα: tumor necrosis factor alpha; IL-17: interleukine 17; MMP: matrix metalloproteinase; ADAMTS: a disintegrin and metalloproteinase with thrombospondin motifs (aggrecanase); MT-MMP: membrane-type MMP; TIMP: tissue inhibitor of matrix metalloproteinase; TGFβ: Transforming growth factor β.

8.2. Possible biomarkers predicting the development, severity and prognosis of scleritis

Several clinical factors are associated with poor prognosis, such as bilateral involvement, necrosis, longer durations of symptoms at diagnosis, and the presence of any systemic autoimmune disease (Wieringa et al., 2013). Hereof, scleritis in patients with GPA or relapsing polychondritis was commonly found to be severe, while scleritis in patients with rheumatoid arthritis was usually moderate, and in patients with SLE was found to be predominantly mild (Sainz-De-La-Maza et al., 2016a; Sainz de la Maza et al., 1995). Furthermore, positive ANCA's were noted to be associated with severe scleritis, most probably due to their specificity for GPA (de Sousa et al., 2011; Hoang et al., 2008). The prognostic value of general blood inflammation markers, such as C-reactive protein or erythrocyte sedimentation rate, is so far not known in scleritis. Previous research did found increased levels of IL-1b, TNFα, IL-22, MMP-9, and IL17 expressing T-cells in blood and/or tear fluid of patients with active scleritis (Palexas et al., 1992; Sainz-de-la-Maza et al., 2016b; Seo et al., 2006). Despite the yet unknown prognostic value, they are potential biomarker candidates. TNFa and IL-22 are produced by Th17 cells, which can be expanded by IL-2, and inhibited by IFNy. Regarding this, one can implicate the role of TH17 cells and IL-22 in the pathogenesis of scleritis. Increased serum levels of IL-22 were also reported in rheumatoid arthritis and associated with an erosive type (Leipe et al., 2011). Furthermore in rheumatoid arthritis, IL-1b showed the ability to stimulate cartilage degradation (Palexas et al., 1992).

Since the pathogenesis of scleritis is far from elucidated, the identification of useful biomarkers is challenging. Obviously, caution is required in the interpretation of potential biomarkers, and their validation in clinical settings is necessary. The so far identified biomarkers only partly provide reliable, and clinically meaningful information for patients with scleritis. This underlies the urgent need for the development of novel biomarkers.

9. Imaging in scleritis

Imaging of inflamed scleral tissue in scleritis has a crucial role in the diagnosis of especially posterior scleritis. Furthermore, imaging may contribute to further understand the pathogenesis of scleritis, especially with current rapidly evolving imaging modalities. Optical coherence tomography (OCT), B-scan ultrasonography (US), ultrasound biomicroscopy (UBM), fluorescein angiography (FAG), indocyanine green angiography (ICG), and magnetic resonance imaging (MRI) represent mostly studied imaging techniques in scleritis (Okhravi et al., 2005; Watson and Romano, 2014; Zur et al., 2016). Using OCT and UBM, the structure of the anterior sclera can be accurately imaged, while FAG and ICG show the (epi)scleral vasculature (Nieuwenhuizen et al., 2003; Watson and Romano, 2014). The posterior sclera, including vasculature, is well imaged using US, MRI, OCT and ICG.

9.1. Anterior segment of the sclera

In inflamed anterior scleral tissue hypo-reflectivity and small inner hypo-reflective spaces were found using both UBM and OCT (Fig. 4). Possible explanations for these hypo-reflective spaces include the infiltration of inflammatory cells, edema, or the unraveling of collagen fibrils, which has been shown in a histopathological evaluations (Christakopoulos, 2017; Heiligenhaus et al., 1998; Kuroda et al., 2017; Shoughy et al., 2015; Watson and Young, 1985; Zur et al., 2016). Thickening of episcleral and scleral tissue in scleritis was repeatedly described. However, a recent study noticed that the thickening was mainly due to a thickened episcleral layer (Fig. 4) (Kuroda et al., 2017). Focusing on the vasculature, FAG and ICG show differences between scleritis subtypes. Diffuse scleritis, which is characterized by diffuse hyperemia of (epi)scleral vasculature and pain, showed extensive leakage of fluorescein on FAG and late leakage on ICG. This implicates an increased permeability of (epi)scleral vasculature. Nodular scleritis is clinically characterized by a single, or multiple hyperemic scleral noduli. ICG showed leakage of the inflamed nodule, and in one patient the intensity, and size of leakage corresponded with clinical condition. Dilated vessels in the inflamed scleral noduli were seen in all patients with FAG, while leakage pattern of the noduli varied (Nieuwenhuizen et al., 2003; Watson and Romano, 2014). Necrotizing scleritis is characterized by thinning of the inflamed scleral matrix. In this subtype a sluggish flow, vascular closure, and vascular obliteration in regions of necrosis were observed with FAG and ICG. Histopathological evidence of vasculitis was previously reported. Nevertheless, the mechanism of vascular damage in scleritis remains unclear.

9.2. Posterior segment of the sclera

B-scan US is commonly used to diagnose posterior scleritis. Sclerochoroidal thickening with high internal reflectivity, and in some cases fluid in Tenon's capsule, the well-known T-sign, can be seen (Agrawal et al., 2016; Biswas et al., 1998; Munk et al., 1993; Okhravi et al., 2005; Wakefield et al., 2013b). MRI can also accurately document scleral enhancement and thickening. OCT showed that the thickening of the posterior wall was preferably due to choroidal thickening (Uchihori et al., 2014). Choroidal involvement was also reported by irregular and delayed choroidal perfusion, and intermediate-/late phase hyperfluorescence at ICG, which was responsive to therapy (Auer and Herbort, 1998). Whether the choroid is the site of initiation, or choroidal inflammation is adjacent to scleral inflammation, remains unknown (Watson and Romano, 2014).

10. Lessons from therapeutic options

The corner stone of the treatment of non-infectious scleritis is immunosuppressive therapy. As a first step patients are treated with non-steroidal anti-inflammatory drugs. A second step is the temporary use of prednisone and/or treatment with disease modifying anti-rheumatic drugs. Methotrexate and mycophenolate mofetil (MMF) were considered to be superior compared to azathioprine. Methotrexate enhances T-cell apoptosis and affects cytokine production, while MMF reduces T-cell and B-cell proliferation, antibody production, and leucocyte transmigration. Azathioprine is an inhibitor of the proliferation of circulating T-cells and B-cells (Beardsley et al., 2013; Daniel Diaz et al., 2016). In addition, cyclosporine, a T-cell replication inhibitor, was reported to be effective. As a third step biologicals and small molecules have enriched the treatment options for scleritis by engaging specific cytokines, cytokine receptors, or cytokine signaling. Several inhibitors of the cytokine TNFα (infliximab, adalimumab) showed beneficial results in small cohorts (de Fidelix et al., 2015). More recently, anti-IL-6R (tocilizumab), anti-IL-1R (anakinra), anti-IL-1β (gevokizumab), and anti-JAK1/3 (tofacitinib) showed effectivity in individual patients (Bottin et al., 2018; Knickelbein et al., 2016; Poelman et al., 2019). Furthermore, anti-CD20 therapy (rituximab) provided positive results, especially in patients with systemic vasculitis (Cao et al., 2016; de Fidelix et al., 2015; You et al., 2018). The effect of anti-CD20 therapy suggest a prominent role of B-cells and the adaptive immune system in the pathogenesis of scleritis, which is supported by the recent recognition of IgG4 related disease in scleritis (Karim et al., 2017b). However, the previously mentioned treatment options engage either T-cells, B-cells or cytokines, suggesting involvement of both adaptive and innate immunity in the pathogenesis of scleritis.

10.1. Novel therapeutic options engaging MMPs

MMPs are potentially responsible for severe necrosis, and in consequence, their inhibition is of interest. Much effort has been put in attempts to engineer synthetic MMP inhibitors, especially in patients with cancer to prevent tumor progression and metastasis (Burrage et al., 2006). However, the effect of synthetic MMP inhibitors in clinical studies was so far disappointing. Interestingly, blockage of inflammatory cells and cytokines could also potentially reduce the production of MMPs (Fig. 3). The anti-TNF inhibitor etanercept has shown to significantly reduce MMP-1 and MMP-9 levels in rheumatoid arthritis and juvenile idiopathic arthritis patients. Adalimumab has shown to decrease the levels of proMMP-1 and proMMP-3 in patients with rheumatoid arthritis (Arends et al., 2011; Basic et al., 2010; Burrage et al., 2006; Catrina et al., 2002; Chen et al., 2019; Weinblatt et al., 2003). The precise data on the effect of anti-TNF therapy, as well as other potential inhibitors of the MMP cascade, are currently lacking in scleritis (Fig. 3).

11. Discussion and conclusion

This review provides up-to-date insight on the pathogenesis of scleritis. We reviewed the currently available knowledge on the origin and maintenance of scleral inflammation, while taking into account new insights from the research field of systemic autoimmune diseases associated with scleritis. Research in this field remains challenging because of the lack of animal models, the scarcity of available human tissue samples, and low prevalence of the disease.

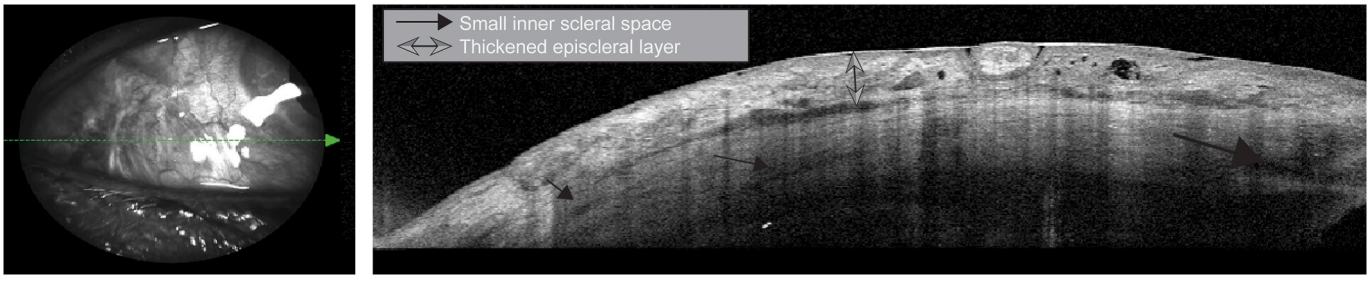

Fig. 4. Optical coherence tomography (OCT) of the anterior segment in a patient with active anterior scleritis. (Epi)scleral thickening, and small inner scleral hyporeflective spaces were reported.

A crucial role for the immune system in the development of non-infectious scleritis is established. Local inflammation of the sclera together with increased inflammatory factors in blood and tears are observed, as well as beneficial responses to immunosuppressive treatment (Palexas et al., 1992; Sainz-de-la-Maza et al., 2016b; Seo et al., 2006). Additional information may arise from knowledge of specific inflammatory processes involved in systemic autoimmune diseases, that are commonly associated with scleritis. The knowledge of HLA and non-HLA gene loci revealed overlap of susceptibility genes in systemic autoimmune diseases and idiopathic scleritis (Deng and Tsao, 2017; Karami et al., 2019; Li et al., 2019; Relle et al., 2016). The potential destructive power of MMPs was studied more extensively in rheumatoid arthritis. MMP-8 may be a key substance in degrading collagen type 1, a major substance of scleral tissue, and the importance of ADAMTS and specific MMPs in the degradation of extracellular matrix PGs was revealed (Burrage et al., 2006). In rheumatoid arthritis, the first attempts to therapeutically target MMPs are performed (Di Girolamo et al., 1997; Seo et al., 2006; Young et al., 2004). However, the pathogenic role of MMPs in scleritis was not yet systematically investigated (Burrage et al., 2006; Rose and Kooyman, 2016).

Although the insight in the pathogenesis of scleritis has improved over the last years, several questions remain unanswered. At first, why does inflammation occur in the sclera, a tissue which is scarcely vascularized? The oscillating blood flow in the suprachoroidal space, resulting from the vascular anastomoses of the choroidal network, provides a likely place for inflammation. It is thereby proposed, and might be the origin of scleral inflammation (Watson and Romano, 2014). Secondly, why does scleritis occur together with systemic autoimmune diseases? A possible explanation is the similar genetic predisposition and/or antigenic similarity between scleral tissue and affected tissues of other organs involved in autoimmune diseases, resulting in so called mimicry hypothesis. The shared components (such as specific collagens and proteoglycans) present in affected tissue may be point of immunological attack and reason for co-occurrence (Orr et al., 2017). As a third, why would some patients with scleritis develop severe necrosis of scleral and adjacent corneal tissue? The collagen destruction is thought to be due to MMPs, however, as previously mentioned, these enzymes are not yet systematically studied in scleritis.

Future research directions

Future investigations in the pathogenesis of scleritis are highly recommended, and include the following subjects of interest. The identification of autoantibodies and/or autoreactive T-cells, and the understanding of the role of MMPs in scleritis. The investigation of gene loci conferring genetic susceptibility may reveal insight in the pathogenesis, and may also provide prognostic information. The assessment of clinically relevant biomarkers in scleritis, and associated systemic autoimmune diseases, and the improvement of imaging techniques may reveal additional information of the disease process, therefore they may improve the clinical management of scleritis. Finally, the development of accurate animal models would be highly relevant, as these are often required to validate hypotheses on pathogenesis. The understanding of the pathogenesis of scleritis has direct implications on its treatment, and might improve therapy, and visual prognosis of this severe and disabling ocular disorder.

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Declaration of competing interest

None.

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