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Targeting the membrane attack complex (MAC)-mediated arm of complement for the diagnosis and treatment of Osteoarthritis

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Introduction

Functionally, the complement system serves to protect the host from pathogens. It is an integral component of the innate immune system that is inextricably linked with the adaptive immune system [1]. Normally the complement system is tightly regulated so that host cells are protected againstoff-target effects or tissue damage whilst being exposed to a pathogenic organism [2].The complement system comprises more than 30 plasma and membrane-bound proteins.It can be activated through three pathways: the classical, the alternative and the lectin pathways. Uncontrolled activation of the complement pathway contributes to the pathogenesis of several autoimmune and inflammatory conditions that include musculoskeletal diseases like Rheumatoid Arthritis (RA) and Osteoarthritis (OA). A complex cytokine network, adipokines, abnormal metabolites, acute phase reactants and the complement system regulate the propagation and progression of inflammation-associated synovitis, cartilage catabolism and bone destruction andconsequently play major roles in arthritis pathophysiology. Synovial tissues (e.g., cartilage and bone)arefrequently degraded in diseases like RA and OAbecause the function of the complement system is compromised [3]. Multiple lines of evidence suggest that low-grade articular inflammation contributes to OA progression. However, it is still unclear whether morphological changes that occur in the OA synovium are primarily due to a systemic immune response or occur secondarily to cartilage degradation and lesions of the subchondral bone.Nevertheless, several components of the complement system are aberrantly expressed inthe synovial fluid of patients with OA, including C1s and C4A (classical pathway), factor B (alternative pathway), C3 and C5 (central component of classical and alternative pathways) and C5, C7, and C9 (terminal complement pathway andmembrane attack complex) [4]. The three distinct activation pathways of the complement system converge at the formation of the C3 and C5 convertases (enzymes that mediate activation of the C5a anaphylatoxin) and at theterminal complement pathway that endsby the formation ofthe Membrane Attack Complex (MAC). CD59 is unique,it is the only complement regulator that inhibits MAC assembly thereby preventing the formation of a lytic pore. While CD59 is normally attached to the cell surface via a Glycosyl Phosphatidyl Inositol (GPI) anchor, it also exists in a number of soluble forms (e.g., in saliva, amniotic fluid and urine) [5]. CD59(protectin) is expressed on the surface of almost all cells (e.g., epithelial, endothelial and hematopoietic cells) and could impact upon homeostasis in synovial tissues [6,7]. In mice, CD59a performs these functions [8]. CD59a is also expressed in almost all tissues [9].The physiological impact of MAC activation upon cartilage andbone has been largely neglected. However, recent studies in mice identified MAC as a potential regulator of cartilage degeneration and osteophyte formation in inflammation-induced models of osteoarthritis, rheumatoid arthritis and age-related bone homeostasis [4,10,11]. In each case tissue injury was increased in the absence of CD59a. This editorial highlights potentially important roles forMAC in the initiation and propagation of osteoarthritis-associated disease phenotypes.

Clinical management of osteoarthritis is largely palliative and there is an ever-growing need for an effective disease modifying treatment. The control of disease progression may rely on the initiation of drug intervention strategies at an early stage in the development of osteoarthritis. Innovative advancements in quantitative imaging techniquesfor diagnostic application in the setting of osteoarthritis may be needed to facilitate the attainment of this goal.Agreater appreciation of the role of MAC and CD59 in the aetiopathology of osteoarthritiscould dramatically help advancement in the diagnosis and treatment of degenerative joint disease.

MAC is strongly expressed in the synovial joint during osteoarthritis

Studies in humans and rodents have charted the progression of osteoarthritis in terms of inflammation, the breakdown of the articular cartilage andaberrant remodelling ofthe underlying bone. These principle hallmarks of osteoarthritis are triggered by multiple factors (e.g., ageing, trauma, obesity and genetics). Modulation of the underlying processes (e.g., age-related tissue degeneration and adipose tissue homeostasis and bone remodelling) by the terminal pathway of the complement system [4,12-14] may be an important when considering the numerous options for drug development.There is little clarity concerning the precipitating and underpinning molecular mechanisms that governthe initiation and progression of osteoarthritis.Therefore, the challenge of discovering a disease-modifying drug for treating osteoarthritis remains. The presence of MAC (comprising the complement effectors C5b-9 was consistently observed, over two decades ago, in synoviumand cartilage from individuals with end-stage osteoarthritisby immunohistochemicalanalysis [15-17]. More recently, proteomic results and ELISA analysis showed that levels of C5b-9 were significantly higher in synovial fluids from individuals with early-stage osteoarthritis than synovial fluids from healthy individuals supporting the notion that terminal complement components occur in synovial joints early in the course of osteoarthritis and persists during the late phases of osteoarthritis [4]. Protein expression of CD59 was also shown on chondrocytes and in the synovial membrane of tissue donors with osteoarthritis [4,18,19]. Cells regulate tissue degeneration during osteoarthritis therefore retain their ability to inhibit of MAC formation, whether this is at the same rate as normal tissues remains to be seen.

Clinical management of OA is largely palliative; opioids, non-steroidal inflammatory drugs and steroid injections are used conventionally to control arthritis-associated pain.Drug design is being facilitated by the increasingly detailed structural understanding of the molecules involved in the complement system and the role of complement in modulating inflammatory and degenerative diseases [18,20]. There exists a strong rationale for targeting the complement system as a disease-modifying therapy for osteoarthritis.

Targeting MAC at sites of complement activation for diagnostic imagingduring osteoarthritis

Over the past two decades there has been a near universal focus on resynchronizing complement by targeting the systemic compartment for therapy. The effects of pathogenic dysregulation of complement almost exclusively occur in the local tissue environment where injury and/or impaired functionmanifest. For diagnosis of diseases such as osteoarthritis there is an opportunity to develop novel molecular imaging strategies by using radiological probes that recognize tissue-bound complement components at sites of pathology.Currently, patient history accompanied byclinical findings from X-rays, Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) scans are commonly used to diagnoseosteoarthritis. X-ray and CT typically detect joint space narrowing, morphological changes in the bone and ectopically formed calcified tissues. These are recognizable changes indicativeof late stage of osteoarthritis progression.Molecular imaging techniques such as immune-positron emission tomography (Immuno-PET) may offer significant advantage beyond the available imaging tools for early diagnosis of osteoarthritis-associated pathology when used to detect complement activation and/or complement mediated damage [21,22]. Antibodies that donot interfere with the wide range of physiologic functions of the complement system maybe most appropriate for clinical utility.

Breakdown of the articular cartilage with remodelling of the underlying bone is the hallmark of OA. Cartilage is avascular and aneural and contains just one cell type, the chondrocyte. Chondrocytes are responsible for maintaining homeostatic cartilage turnover by responding to changes in the mechanical and inflammatory environment within the joint. The complement cascade is crucial to the pathogenesis of OA in that complement activation (irrespective of the trigger) results in the formation of MAC on chondrocytes, which in turn either kills the cells or causes them to produce matrix-degrading enzymes and inflammatory mediators. This provides a rationale for targeting MAC as a disease-modifying therapy for OA because all these effectors promote joint pathology. Specific pharmacological agentsaimed at the resynchronization of the terminal complement pathway for the treatment of OA may be a realistic future vision.The success of any approach would likely be contingent upon targeted local inhibition of the C5b-9 complex or MAC within the joint space rather than systemic blockade that would compromise thepatient's immune defence against invading pathogens. There are currently only two anti-complement drugs on the market (Eculizumab andC1-INH). However, many more are being developed for a broad spectrum of diseases that include infectious, inflammatory, degenerative, traumatic and neoplastic disorders. The history, current landscape and future directions for anti-complement therapies was reviewed by Morgan and Harris in 2015 [21].

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