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Review

Complement involvement in bone homeostasis and bone disorders

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ABSTRACT

An integral part of innate immunity is the complement system, a defence system, consisting of fluid-phase and cell surface-bound proteins. Its role to ensure adequate responses to danger factors and thus promoting host defence against pathogens has been well described already for decades. Recently, numerous further reaching functions of complement have been discovered, among these are tissue homeostasis and regeneration, also with respect to the skeletal system.

The influence of complement activation on bone was recognised first in pathological conditions of inflamed bone tissue and surrounding areas, observed, for example, in rheumatoid arthritis and osteoarthritis. Greatly enhanced levels of complement proteins were detected in synovial fluids and sera of arthritic patients compared to healthy individuals. Additionally, complement-mediated signalling was shown to modulate periodontitis disease development and progression. Periodontitis is an infectious condition of the periodontium, which involves severe bone loss. Moreover, the complement system critically modulates bone regeneration and healing outcome after fracture. This is seen in uneventful fracture healing, but particularly under severe inflammatory conditions induced by an additional traumatic injury. Therefore, complement activation plays an important role in both sterile and non-sterile inflammatory conditions of the bone, which will be addressed here in respect of findings in bone fractures, arthritides, periodontitis and osteomyelitis.

Importantly, complement proteins are thought to be critical not simply in the states of an activated immune system, but also for bone growth during physiological development and bone homeostasis, given for example their presence in long-bone growth-plate cartilage. Furthermore, bone-cell development from precursor cells and bone-cell metabolism and communication, for example, between bone-forming osteoblasts and bone-resorbing osteoclasts, are dependent on or even critically influenced by the presence of complement proteins and complement-mediated signalling.

The present review summarises the current view on the role of the complement cascade on bone, both under homeostatic physiological conditions and under inflammatory and infectious conditions, which strongly affect the bone and skeletal health. Furthermore, this review addresses the potential and the feasibility of therapeutic interventions involving the complement cascade, derived from experimental and clinical data. Modulating the complement system could help in the future to reduce bone infections, ensure a balanced bone turnover and to generally improve skeletal health.

1. Introduction

The complement system (Fig. 1) is an evolutionary ancient system and an integral part of innate immunity, which is crucial for host defence against endogenous danger molecules and invading pathogens. It is immediately activated by coming into contact with pathogen- and danger-associated molecular patterns (PAMPs and DAMPs), and a cascade of protease-based cleavage and activation processes is initiated [1,2]. Through this process, chemoattracting molecules are generated, which recruit and activate innate immune cells, resulting, for example, in the production of inflammatory cytokines. Moreover, opsonins enabling facilitated phagocytosis of pathogens and protein complexes promoting foreign cell lysis are important complement components in ensuring host protection. The complement cascade can be activated by different molecules, including bacterial cell-wall components and antigen-antibody complexes, resulting in the activation of one of the three main complement pathways, namely the classical, alternative or lectin pathways [3]. Common to all three modes of complement activation is

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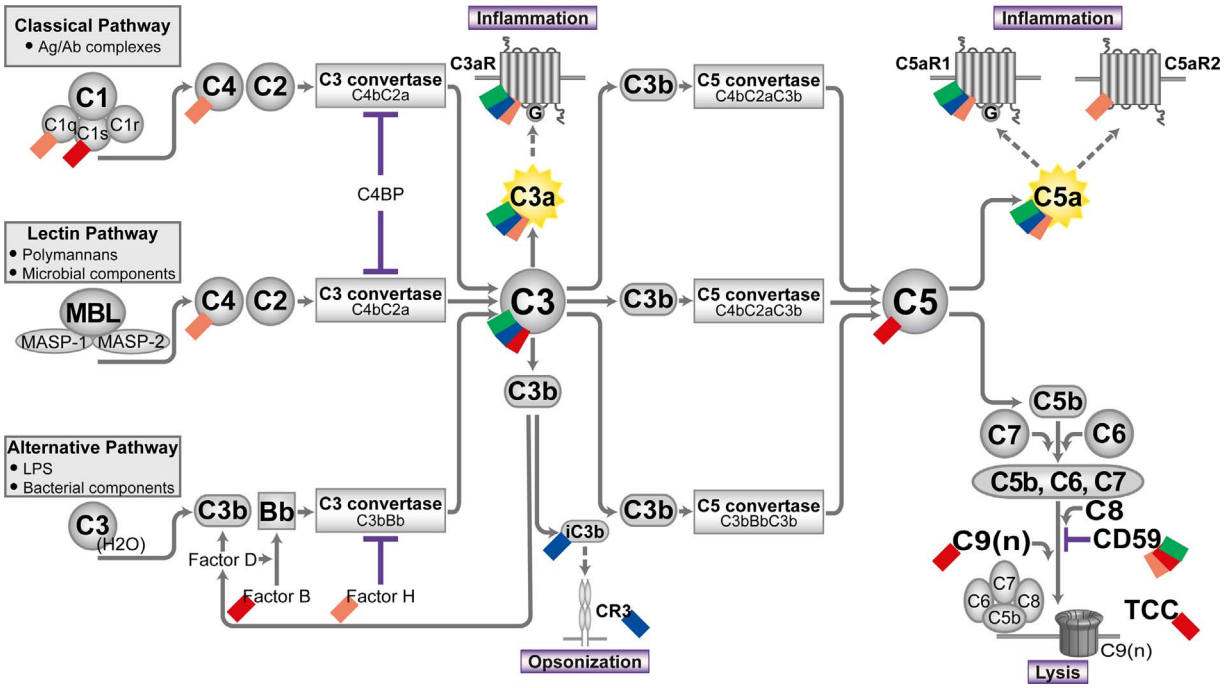

Fig. 1. Physiological contribution of complement proteins to bone growth and metabolism under homeostatic conditions.
Colour coding indicates the involvement of specific complement proteins in endochondral ossification (red), osteoclastogenesis (green), osteoblastogenesis (orange) and cell–cell communication between osteoblasts, osteoclasts and mesenchymal stem cells (blue). Ag: Antigen, Ab: Antibody, LPS: Lipopolysaccaride, G: G-protein, MBL: Mannose-binding lectin, MASP: Mannan-binding lectin serine protease, TCC: Terminal complement complex.

the generation of a C3 convertase, cleaving C3 into C3a and C3b [4]. While the smaller fragment C3a, an anaphylatoxin, acts directly pro-inflammatory, for example, by promoting neutrophil respiratory burst [5,6], C3b can act as an opsonin and, more importantly, is a building block of the alternative pathway (AP) C3 and C5 convertases as well as of the classical C5 convertase [7]. C5 cleavage is then catalysed by C5 convertase and the resulting products are the two crucial complement mediators C5a and C5b (Fig. 1).

The anaphylatoxin C5a acts similarly to C3a as a pro-inflammatory mediator [8,9], and initiates important downstream effects via binding to its receptors C5aR1 (CD88) and C5aR2 (C5L2) [10]. C5b, by contrast, is an important subunit of the terminal complement complex (TCC), which is built upon the sequential assembly of the complement components C6, C7, C8 and several C9 molecules [11,12]. This poly-molecular C5b-9 protein complex can promote tissue destruction by its lytic activity on cells [13], but can also exert cell-modulating effects when present sublytically or in its soluble form (sC5b-9) [14,15]. To ensure host-cell protection from TCC-mediated cell lysis, the complex is controlled by regulatory proteins, including CD59, clusterin and S protein [14] (Fig. 1).

The main proportion of complement proteins is generated in the liver and then released into the bloodstream, where fluid-phase complement-cascade activation mainly takes place. Nevertheless, several extra-hepatic tissues and cell types, including fibroblasts, endothelial cells and immune cells, are also able to generate complement components locally at the tissue site [16,17]. Therefore, in addition to the beneficial functions regarding host defence and pathogen clearance, locally and systemically activated complement can contribute to disease development and progression, which is currently well recognised, although frequently poorly understood. The pathomechanistic role of the complement system has been discussed in relation to numerous inflammatory, infectious and autoimmune disorders, including trauma, ischemia, sepsis and systemic lupus erythematosus, where complement hyper-activation was found to be a major contributory factor to the loss of tissue integrity and to tissue destruction [18,19].

Moreover, in addition to the well-described actions in immune response and inflammation, far more extensive functions have been attributed to the complement system in recent decades, including the regulation of haematopoiesis, coagulation, waste disposal, reproduction, development and regeneration [20–23]. Novel functions have also been described in tissue homeostasis and repair [24], such that the complement cascade is currently no longer regarded as merely a mediator and effector of innate immunity [25].

There is growing evidence that the complement system has an impact on the skeletal system. Hereby, complement regulates bone metabolism and turnover both under physiological and pathophysiological conditions. Indeed, the state of complement activation was found to influence and modulate the development and progression of several bone-related acute and chronic inflammatory disorders.

Particularly in chronic inflammatory disorders, including rheumatoid arthritis (RA), periodontitis and osteomyelitis, all of which involve severe bone loss, the complement system has a generally well-described impact, as reviewed here. Additionally, in bone regeneration after bone injury, including fracture, the hereby-involved cells are dependent on balanced complement activation. Research thereon comprises, among others, the relative impact of complement components activated early or late in the cascade, the role of the three main complement-activation pathways and, in particular, the contribution of cleavage products of complement components C3 and C5 to bone dysfunction.

Therefore, the scope of the present review is to dissect the so far unappreciated role of complement in bone development and metabolism as well as bone regeneration after fracture. Moreover, the impact of complement activation on septic and aseptic inflammatory disorders of the skeletal system will be discussed, in particular RA, periodontitis and osteomyelitis.

2. Complement influences bone growth and bone cell differentiation

Bone is an important tissue in providing a framework and mobility for the body and structural support for internal organs. The skeleton is involved in the metabolic turnover of calcium and phosphate, and is