Editorial

Enigmatic femoral growth by loss of complement regulator CD59a

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Comment on: Bloom AC, Collins FL, Van't Hof RJ, *et al.* Deletion of the membrane complement inhibitor CD59a drives age and gender-dependent alterations to bone phenotype in mice. Bone 2016;84:253-61.

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The paper "Deletion of the membrane complement inhibitor CD59a drives age and gender-dependent alterations to bone phenotype in mice" by Anja C. Bloom *et al.* in *Bone* 2016 (1) describes for the first time an increased femur length and cortical bone volume (with reduced mineral density) in male mice deficient in CD59a. It appears that the role of CD59a, which inhibits the assembly of the membrane attack complex (MAC) and thereby the terminal complement activation pathway (2), was rather underestimated in the past regarding bone tissue development and function.

Concerning the bone growth it would be of interest if other bones than the femur are affected in absence of CD59a, such as the humerus or vertebral bodies? It is remarkable, that in the study by Bloom *et al.* the CD59-dependent bone alterations were only found in male but not in female mice, and were associated with an increased bone resorption and mineral apposition rate, and furthermore with enhanced *in vitro* osteoclastogenesis. Reasons for the highly CD59a-dependent sex difference of the femur length have been carefully addressed in the discussion section e.g., the enhanced complement activity in males in comparison to females, which might cause enhanced discriminatory effects; or the well-known estrogen-induced inhibition of the osteoclastogenesis, which could counteract the CD59a-associated elevated osteoclastogenesis in females. However, the effect remains somehow enigmatic unless a direct definite mechanism has been provided. Osteoclastogenesis assays in this publication revealed an increased generation of the inflammatory mediator Mkc (CXCL1) in response to M-CSF in absence of CD59a, but sex differences have not been displayed. A possible direct interaction, regulation or common up- or down-stream signaling route of CD59 and estrogens is so far missing and might present a future research target. It is noteworthy, that blockade of estrogen by tamoxifen or faslodex in breast cancer therapy, has been shown to result in highly up-regulated CD59 on tumor cells, indicating not only the attempt of evasion of immune-surveillance by breast tumor cells in general and limiting complement-dependent cell killing by anti-estrogens, but also some cross-talk between estrogens and CD59 (3). Again, the exact underlying mechanisms remain in the dark.

Future experiments should certainly define the growth factors being expressed or modulated by blockade of MAC. On the cellular level, *in vivo* effects of mesenchymal stem cells (MSC) as precursors of osteoblasts—known to express both, complement receptors and also complement regulatory proteins such as CD59 (4)—may contribute to an altered bone phenotype in the absence of CD59a. Especially during osteogenic differentiation CD59 mRNA expression was found to be significantly up-regulated in comparison to undifferentiated MSCs (5). Furthermore, mature osteoblasts and to a lesser extent osteoclasts expressed CD59 (5), which might induce or regulate bone homeostasis beyond the defense function against "auto-aggressive" complement attacks. Since CD59 is expressed in numerous cell types that might directly or indirectly influence the bone phenotype, experimentally, a selective targeted blockade or knock down of CD59a in either osteoblasts or osteoclasts might help to define the contribution of CD59 in surrounding and remote

cells and might define novel functions of CD59.

Overall, these interesting results of a sex-dependent bone phenotype in CD59a-deficient mice wait to be translated to the clinical setting e.g., in patients with acquired or congenital CD59 deficiency, such as paroxysmal nocturnal hemoglobinuria (PNH) or congenital isolated CD59 deficiency (6). Furthermore, expansion of these findings to the development of posttraumatic and non-traumatic osteoarthritis is tempting. Although no information on the sex allocation is provided, the data from Wang *et al.* showed histomorphological evidence that MAC inhibition may result in beneficial effects during osteoarthritis development (7). Accordingly, the absence of CD59 aggravated signs of osteoarthritis. The present paper may now put a new light on those results since CD59 deficiency could have also altered bone phenotype before any intervention and differently shaped the subsequent osteoarthritic response (7). Thus, the role of CD59 needs to be further scientifically and clinically addressed for its potential to beneficially modulate bone homeostasis, osteoclast function, fracture healing (8) and growth.

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Footnote

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