Review of: "Aged bone matrix-derived extracellular vesicles as a messenger for calcification paradox"

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Extracellular vesicles: an important cargo of miRNAs from aging bone to calcified vessels

Osteoporosis and vascular calcification are very common among aging people. In osteoporosis, the imbalance between osteoblastic and adipogenic differentiation of bone marrow mesenchymal stromal cells (BMSCs), namely reduced bone formation and increased adipocyte production mainly contributed to the decreased bone quality and quantity. However, in vessels there is another different story. Vascular smooth muscle cells (VSMCs), which share many common features with BMSCs lead to vascular calcification which is somewhat similar to bone formation. Therefore, clinically the calcification paradox remains mysterious and interesting for decades. How do two tissues sharing similar remodeling mechanisms show so different results in senescence. Extracellular vesicles give us an answer.

Fat-bone imbalance: BMSCs differentiation shift

BMSCs are common progenitors of osteoblasts and adipocytes in bone marrow[1]. In aged bone, BMSCs tend to differentiate into adipocytes instead of osteoblasts, which leads to accumulated adiposity and reduced bone formation [2,3]. The imbalance of BMSCs differentiation is a major cause of osteoporosis [4-6]. Recent studies have shown that osteoporosis is often accompanied by an increase in bone marrow adipose tissue [7]. Another research has demonstrated that patients with osteoporosis have decreased numbers of osteoblasts [8] and increased numbers of adipocytes in the bone marrow [9].The decreased ability of BMSCs to generate osteoblasts makes them more likely to generate adipocytes, leading to age-related osteoporosis and fragility fractures [10]. Modulating the differentiation fate of BMSCs is a therapeutic option for osteoporosis.

Vascular calcification: VSMCs phenotype transition

Vascular calcifications featured by calcium mineral deposits are common among individuals over 60 years old. Intrinsic stiffness of VSMCs is aggravated with aging [11]. Calcification has been shown to be an active process driven in part by the trans-differentiation of VSMCs within the vessel wall [12]. The current view is that there are two main types of vascular calcification, namely intimal and medial calcification.The osteo/chondrogenic conversion of VSMS is the most intensively studied phenotypic transition, which plays important role in orchestrating VC of both the intima and media. Under normal healthy conditions, VSMCs control arterial stiffness by over-producing different ECM constituents, such as elastin, and collagen, which provides the biomechanics, structural integrity, and signaling regulation of ECM and then maintain vascular homeostasis [13]. Moreover, VSMC initiate osteogenic differentiation and mineralization in response to various stimuli, thereby driving VC.

The calcification paradox

Osteoporosis, the most common degenerative bone disease, is a systemic disease characterized by low bone mass and density, which is prone to brittle fracture [14-16]. One important cause of osteoporosis is decreased calcification capacity. On the other hand, VC has long been considered a passive and degenerative process and is a recognized risk factor of cardiovascular morbidity and mortality. Currently, it has been currently considered to be an active process with pathological features, mineral components, and bone formation processes. Interestingly, patients with osteoporosis always have VC. How does decreased calcification in bone and increased calcification in vessels occur simultaneously?

Traditionally, osteoporosis and VC have been considered as independent diseases related to age. However, recent studies have shown a strong relationship between osteoporosis and VC. Both of them are independent of age and with common risk factors and pathophysiological mechanisms [17]. Therefore, the treatment of osteoporosis may affect the VC progression, and vice versa. In conclusion, a better understanding of the paradox between these two diseases is important in order to propose better treatment strategies in an increasingly aging situation.

Extracellular vesicles: the key to the paradox

OP and VC are two pathological phenomena which seriously threaten the health of elderly people. The traditional theory holds that OP and VC are two independent events of calcium and phosphorus metabolism disorders. Xie et al. [22] demonstrated that aged bone matrix derived EVs (AB-EVs) are bone-derived messenger in the calcification paradox of bone and blood vessels in aging body. EVs could regulate the physiological and pathological processes due to their characteristics of loading bioactive molecules [18-21]. Here, Xie et al.[22] further verified that AB-EVs prefer BMSC adipogenesis instead of osteogenesis and augment calcification of VSMCs by transporting miR-2861 and miR-483-5p (Figure.1). In recent years, studies have found that bone is not only an "inert organ" that is regulated by nerves and body fluids, but also an "endocrine organ" that participates in the regulation of body homeostasis [23]. This study further confirmed that EVs carrying a variety of signaling molecules are important nanocarriers for skeletal cells to regulate body functions, expanding our understanding of the regulation of bone metabolism and trans-organ metabolism of bone-derived substances.

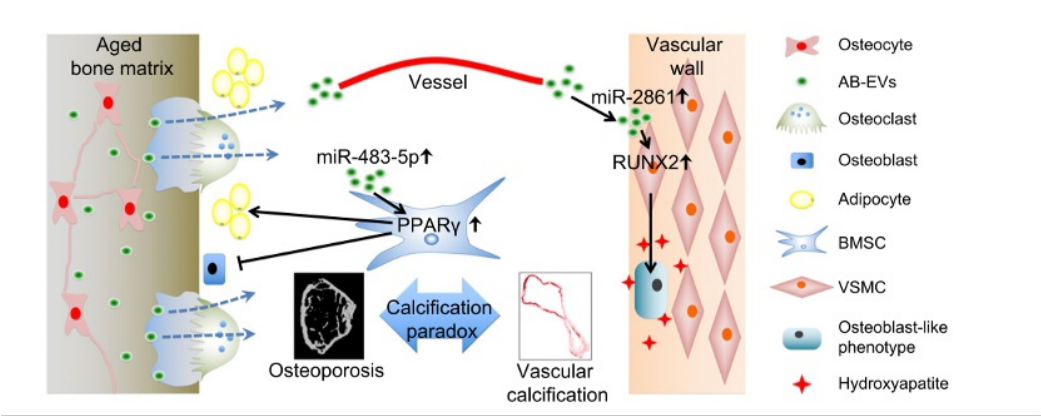

Figure 1 The schematic diagram showing the role of AB-EVs as a messenger for calcification paradox[22]. Copyright 2022

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