Review

The "love–hate" relationship between osteoclasts and bone matrix

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Abstract

Osteoclasts are unique cells that destroy the mineralized matrix of the skeleton. There is a "love–hate" relationship between the osteoclasts and the bone matrix, whereby the osteoclast is stimulated by the contact with the matrix but, at the same time, it disrupts the matrix, which, in turn, counteracts this disruption by some of its components. The balance between these concerted events brings about bone resorption to be controlled and to contribute to bone tissue integrity and skeletal health. The matrix components released by osteoclasts are also involved in the local regulation of other bone cells and in the systemic control of organismal homeostasis. Disruption of this regulatory loop causes bone diseases, which may end up with either reduced or increased bone mass, often associated with poor bone quality. Expanding the knowledge on osteoclast-to-matrix interaction could help to counteract these diseases and improve the human bone health. In this article, we will present evidence of the physical, molecular and regulatory relationships between the osteoclasts and the mineralized matrix, discussing the underlying mechanisms as well as their pathologic alterations and potential targeting.

Introduction

Osteoclasts and bone matrix have a "fatal attraction" by which osteoclasts interact with the mineralized substance (Fig. 1), with the ultimate goal to destroy it [1]. However, at the end of the resorption phase osteoclasts die, thus completing a deadly loop, which, however, is physiologically indispensable for harmonic skeletal growth and fitness [1]. What makes this attraction fatal is not fully understood and several mechanisms have still to be elucidated for a comprehensive understanding of osteoclast and bone matrix biology. In this review, we will discuss what is known about the osteoclast-to-bone matrix relationship and will speculate on some prospective aspects that will need substantial experimental evidence to be definitively proven.

How does the osteoclast recognize the bone matrix?

A bone-resorbing osteoclast is a polarized cell, characterized by the basolater membrane domain facing the vascular compartment and presenting an apical domain with a functional secretory activity, and by the membrane domain facing the bone matrix, which includes the innermost ruffled border domain and the outermost sealing domain [2]. The ruffled border is formed by a peripheral fusion area where lysosomal membranes fuse with the plasma membrane secreting enzymes and inserting ion transporters essential for mineral dissolution, and a central uptake area implicated in the endocytosis of the degraded bone matrix components [2].

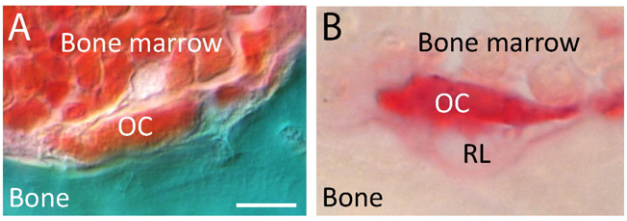

Fig. 1. Histological sections of mouse tibias. (A) Goldner's Masson trichrome stain showing the tight interaction of an osteoclast (OC) with the bone matrix. (B) Tartrate-resistant acid phosphatase histochemical staining (purple) of a resorbing osteoclast (OC) and the underneath resorption lacuna (RL). Bar = 25 μm.

The "love" of the osteoclast for the mineralized matrix relies on its sealing membrane, which is endowed with podosomes, short cellular protrusions, 1 μm wide and 0.6 μm high [3,4]. The dynamic structure of podosomes makes them ideal adhesions for a cell-to-matrix interaction that requires quick assembly/disassembly cycles compatible with the mechanisms of bone resorption [4]. Through the podosomes, the sealing membrane ensures the extracellular compartment located between the osteoclast and the resorbing matrix is segregated from the rest of the environment, in order to preserve a peculiar and highly controlled composition [1].

Early studies identified podosomes in osteoclasts [3] (Fig. 2), macrophages [5,6] and invasive tumor cells [7]. The latter of these were termed invadopodia [8]. Podosomes and invadopodia share several molecular mechanisms [9] and the peculiar ability to promote adhesion to the mineralized matrix [10] or to digest the extracellular matrix in order to invade the tissue [11], respectively.

Podosome dynamism is ensured by a series of structural and signaling molecules very much sensitive to environmental changes. They include actin microfilaments, actin binding proteins (i.e. fimbrin, α-actinin), actin branching proteins [i.e. cortactin, Arp2/3 complex, Neuronal-Wiskott Aldrich Syndrome Protein (N-WASP), and WASP-interacting protein (WIP)] [12–13], adhesion proteins (i.e. talin, vinculin, paxillin, tensin) [3], microfilament-severing molecules (i.e. gelsolin, cofilin) [14], small GTP-binding protein (i.e. Rho) [15] and guanine exchange factors (i.e. Dock5 and vav3) [16], and a number of ubiquitin ligases (i.e. c-Cbl and Cbl-b), tyrosine kinases (i.e. c-Src, PYK2, Abl, FAK) [17–19] and phosphatases (i.e. PTPα, PTPε, SHP2). These components are the "elixir of love" and contribute to pro-survival signals, triggering osteoclast polarization, bone resorption and dynamic regulation of podosome assembly/disassembly [19–23]. Interestingly, in order for podosomes to efficiently attach the osteoclast to the substrate and seal the resorption lacuna, they have to be located in a continuous peripheral annulus coinciding with the sealing membrane. Due to the enormous number of podosomes herein organized, this annulus is called actin ring [4] and during bone resorption each osteoclast may display multiple actin rings, each of which matching with an underneath resorption lacuna [24].

Podosome dynamism is essential for rapid morphological changes during the entire phase of bone resorption. In vitro studies have provided evidence that osteoclasts are able to alternate resorption and motility phases, with a kind of "hit and run" mechanism, which is responsible for tunneling through the bone cortex as well as for excavating resorption trail surfaces that are the result of multiple resorption cycles [24]. Therefore, it is believed that

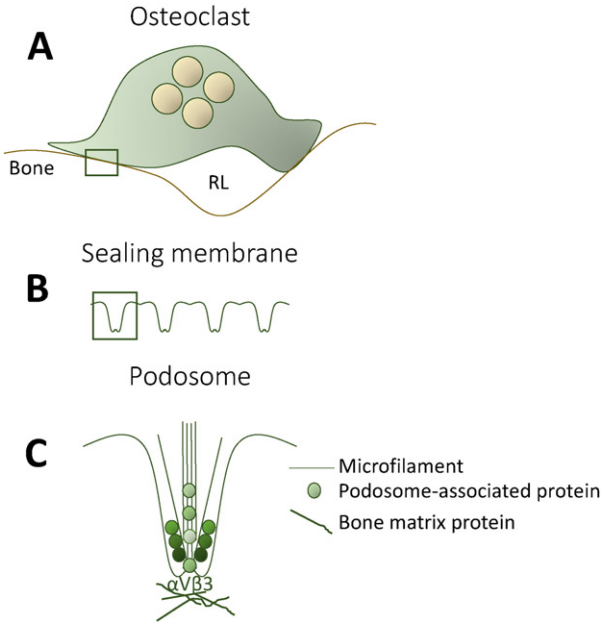

Fig. 2. Cartoon illustrating osteoclast adhesion and podosomes. (A) A polarized osteoclast and its adhesion to the bone matrix. Box: sealing membrane area enlarged in (B). RL: resorption lacuna. (B) The sealing membrane of the osteoclast presents several foot-like protrusions called posodomes. Box: single podosome enlarged in (C). (C) Each podosome presents a core of microfilaments, several associated proteins (i.e. acting-binding, adhesion, signaling, regulatory proteins), and the αVβ3 integrin linking the podosomal cytoskeleton to the extracellular matrix.