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Leading Opinion

Bone bonding at natural and biomaterial surfaces ☆

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Abstract

Bone bonding is occurring in each of us and all other terrestrial vertebrates throughout life at bony remodeling sites. The surface created by the bone-resorbing osteoclast provides a three-dimensionally complex surface with which the cement line, the first matrix elaborated during de novo bone formation, interdigitates and is interlocked. The structure and composition of this interfacial bony matrix has been conserved during evolution across species; and we have known for over a decade that this interfacial matrix can be recapitulated at a biomaterial surface implanted in bone, given appropriate healing conditions. No evidence has emerged to suggest that bone bonding to artificial materials is any different from this natural biological process. Given this understanding it is now possible to explain why bone-bonding biomaterials are not restricted to the calcium–phosphate-based bioactive materials as was once thought. Indeed, in the absence of surface porosity, calcium phosphate biomaterials are not bone bonding. On the contrary, non-bonding materials can be rendered bone bonding by modifying their surface topography. This paper argues that the driving force for bone bonding is bone formation by contact osteogenesis, but that this has to occur on a sufficiently stable recipient surface which has micron-scale surface topography with undercuts in the sub-micron scale-range.

Keywords: Bone bonding; Cement line; Biomineralisation; Calcium phosphate; Bioactive; Implant

1. Introduction

Bone bonding, or the ability of bone tissue to bond to the surface of a synthetic material, was a term first introduced into the biomaterials lexicon following the exciting experimental findings of Hench et al. [1] in the early 1970s on tissue bonding to bioactive glasses. However, the biological phenomenon of bone bonding is as old as the normal remodeling of bone itself; a tissue which can be traced back in evolution to the agnatha of the early middle Paleozoic Era (543–248 million years ago) [2]. Indeed, because the extensive calcium phosphate cranial exoskeleton of these jawless protofish is preserved in the fossil record, we can track the evolution of our calvariae and demonstrate that our bone tissue has been evolving considerably longer than we have existed as a genus (*Homo*)! It is therefore startling that attempts to deconvolute the mechanisms of bone bonding have, generally, focused on the surface properties of biomaterials rather than the underlying biology which is the driving force for the phenomenon.

To achieve an understanding of bone bonding, my approach herein is twofold:

First, I describe the resorption surface created by an osteoclast in bone and the initial matrix synthesis which occurs during de novo bone formation at such a natural bone remodeling site. Thus, without unnecessary repetition of information which can be gained by other reviews of the broader biological cascades of bone remodeling [3,4], the focus herein is on the structure of the resorbed bone surface

☆ *Note*: Leading Opinions: This paper provides evidence-based scientific opinions on topical and important issues in biomaterials science. They have some features of an invited editorial but are based on scientific facts, and some features of a review paper, without attempting to be comprehensive. These papers have been reviewed for factual, scientific content.

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and the important "cement line" extracellular matrix that occupies the interface between new bone and old bone during such remodeling.

Second, I address, from a somewhat phylogenetic perspective, the conservation of the cement line and its relevance to our understanding of bone bonding to biomaterial surfaces. My aim here is not to provide treatises on either bone cell biology, or bone phylogeny, but to demonstrate that the cement line is a highly conserved extracellular interfacial matrix which has evolved to anchor new bone tissue, of which it is an integral part, to the highly three-dimensionally complex sub-micron scale surface of bone tissue created by an osteoclast; and that this biology can be recapitulated at the implant surface.

My underlying thesis is that it is only by understanding such fundamental biological processes that one can begin to comprehend how bone can bond to synthetic biomaterials and, critically, what surface features of such biomaterials are important in permitting bone bonding to occur. This argument is an extension of four previous reviews, on the principals of peri-implant bone healing, in which we have provided the foundations for what is discussed herein [5–8].

2. The bone remodeling process

Bone is a bloody, dynamic, living tissue that changes throughout life. Like other connective tissues of the body, bone comprises cells embedded in an abundant extracellular matrix. However, unlike most other connective tissues the extracellular matrix is mineralized to bestow unique physiological functions. As the major structural element of the skeleton, bone provides not only locomotor support and protection, but also a dynamic mineral and protein reservoir. The constant remodeling of bone tissue provides a mechanism for scar-free healing and regeneration of damaged bone tissue and also plays, through endocrine control, a vital role in the calcium and phosphate balance of the body fluids.

Bone remodeling is achieved through the resorptive activity of osteoclasts and the synthetic activity of osteoblasts. These two cell populations are constantly responsible for the turnover, at any one time, of approximately 3–5% of the human skeleton. Perturbations of this cellular activity, resulting in an imbalance between the activities of the two cell types, are the key element in many bone metabolic diseases, disuse atrophy, and microgravity-induced osteopenia. The process of remodeling of human bone can be witnessed histologically as soon as the first bone is formed (approximately 6 weeks in-utero) and continues throughout life, although the rate of remodeling decreases with age.

As stated above, it is not the purpose of this review to focus on the molecular and biochemical activities of the cells responsible for this remodeling process. But, there are two specific issues that receive little attention in the bone biology literature and are of considerable importance from a biomaterials perspective. These are discussed below.

2.1. The bone surface created by osteoclasts

When osteoclasts resorb bone, which is known to be a two phase process of both the dissolution of the inorganic matrix and enzymatic degradation of the organic components, the result is the creation of a demineralized bone matrix which becomes the recipient surface for new bone formation. While it is common, for reasonable reasons of graphic expediency, to represent an osteoclast sitting on the surface of bone with its ruffled membrane of the resorptive organ falling into the resorption lacuna below the cell [9], such cartoons do not represent the biological reality where it has been reported that the ruffled membrane with its invaginated surface penetrates the bone matrix to a depth of approximately 1 μm [10]. This morphological feature of the osteoclast/bone matrix interface is important because it results in the demineralized collagen of the bone matrix presenting a resorption surface of three-dimensional complexity at the sub-micron scale range. Thus, the floor of a Howship's lacuna, a histological feature that can be visualized at the light microscopic level and which measures tens or even hundreds of microns in cross section, is highly topographically complex at the sub-micron level (Fig. 1).

Furthermore, because of the varying orientation of the collagen fiber bundles in bone, not only is this three-dimensional structure highly variable but it can also present a surface with undercuts. This morphological feature of the resorbed bone matrix is important because it presents a surface of three-dimensional complexity, at the sub-micron scale range, into which the matrix of the cement line can be deposited to form an anchoring mechanism of new bone to old. Thus, in normal bone remodeling, the resorption surface of old bone provides a highly topographically complex surface into which new bone matrix will be deposited, and with which the latter can interdigitate and interlock. Despite this, it is the opinion of some, based on in vitro experiments, that osteoblasts digest the remaining demineralized collagen in the osteoclast resorption lacuna prior to elaborating new collagen directly on the old bone surface [11]. However, this opinion completely fails to provide an explanation for the formation of a collagen-free cement line interface.

2.2. Elaboration of the cement line interface

The existence of this interfacial matrix has been known since the early observations of von Ebner who, in 1875, first reported that osteons were demarcated from the surrounding bone by a distinct matrix, which he called "Kittlinien" (Engl: cement line) suggesting the biological function of cementing a secondary osteon to the surrounding bone matrix [12]. However, it was more than a century