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Review

OsteoMacs: Key players around bone biomaterials

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ABSTRACT

Osteal macrophages (OsteoMacs) are a special subtype of macrophage residing in bony tissues. Interesting findings from basic research have pointed to their vast and substantial roles in bone biology by demonstrating their key function in bone formation and remodeling. Despite these essential findings, much less information is available concerning their response to a variety of biomaterials used for bone regeneration with the majority of investigation primarily focused on their role during the foreign body reaction. With respect to biomaterials, it is well known that cells derived from the monocyte/macrophage lineage are one of the first cell types in contact with implanted biomaterials. Here they demonstrate extremely plastic phenotypes with the ability to differentiate towards classical M1 or M2 macrophages, or subsequently fuse into osteoclasts or multinucleated giant cells (MNGCs). These MNGCs have previously been characterized as foreign body giant cells and associated with biomaterial rejection, however more recently their phenotypes have been implicated with wound healing and tissue regeneration by studies demonstrating their expression of key M2 markers around biomaterials. With such contrasting hypotheses, it becomes essential to better understand their roles to improve the development of osteo-compatible and osteo-promotive biomaterials. This review article expresses the necessity to further study OsteoMacs and MNGCs to understand their function in bone biomaterial tissue integration including dental/orthopedic implants and bone grafting materials.

1. Introduction

Monocytes and macrophages are some of the most abundant cell type found in the bone marrow. Furthermore, they represent the first cell types that interact with foreign pathogens and implanted medical devices. Classical studies have demonstrated that macrophages are rapidly recruited to infectious and injury sites where they play critical roles in innate immunity. Here they demonstrate broad roles and are responsible for regulating tissue homeostasis including innate and adaptive immunity, wound healing, hematopoiesis and malignancy [1].

Based on their crucial and distinct roles in tissue homeostasis and immunity, they are attractive therapeutic targets for a broad range of pathologies. Furthermore, they are key players in tissue integration of various biomaterials across a wide range of tissues. Yet the field of bone-biomaterial biology has largely omitted their importance over the years. For instance, a recent systematic review of dental and orthopedic implants found that over 90% of research in this area focused primarily on in vitro behavior of osteoblasts on implant surfaces while only a small percentage (roughly 10%) was dedicated to immune cells including monocytes, macrophages, osteoclasts, leukocytes and multinucleated giant cells (MNGCs) [2]. With the advancements made in the field of osteoimmunology, it becomes vital to better understand the response of these cell types to various bone biomaterials. Immune cells play a pivotal role in determining the in vivo fate of bone biomaterials by either facilitating new bone formation around bone-implanted devices but have also been associated with creating an inflammatory fibrous tissue encapsulation. It is now understood that macrophages are the major effector cell in immune reactions to biomaterials where they are indispensable for osteogenesis. Knockout models have demonstrated that a loss of macrophages around bone grafting materials may entirely abolish their osteoinductive potential, thus confirming their primary role in the immune system modulation later responsible for guiding osteogenesis [3].

Over the years, complex studies from basic research have revealed the dynamic interactions between the skeletal system and immune system [4–6]. It has been shown that a population of

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tissue macrophages named “OsteoMacs” resides within bone as a distinctive canopy structure overlying mature osteoblasts [6]. Although initial bone fracture healing experiments have been characterized by infiltration of inflammatory cells, most of these initial studies focused primarily on the secretion of various cytokines and growth factors important for the inflammatory process including cell recruitment [7–9] and neovascularization [10]. Although macrophages in general have been implicated as key contributors to inflammation, a series of experiments have also revealed their essential roles in bone repair with recent findings demonstrating that even MNGCs may be categorized with a tissue repair phenotype by demonstrating release of M2-related cytokines and growth factors [11]. Thus, the differentiation of monocytes towards M1 or M2 macrophages, as well as their fusion to osteoclasts or MNGCs in response to various biomaterials remains extremely poorly understood. Furthermore, the main factors responsible for directing their phenotypes towards more specialized cell-types in response to biomaterials also remains poorly characterized.

Human histological samples from our dental clinic using a variety of bone grafting materials for bone augmentation procedures have consistently shown a substantially high number of MNGCs around bone substitute materials grafts in stable situations harvested years after original surgeries were performed [12]. Furthermore, a select class of bone substitutes grafts consistently associated with higher than average maintenance of bone mass in grafted sites, are routinely found with significantly higher numbers of MNGCs (Fig. 1). This has led our research team to further question the role of MNGCs on biomaterials as these cells were once thought to only contribute to the foreign body reaction [11]. Interestingly, studies investigating atherosclerotic plaque have provided evidence that macrophages very commonly fuse into MNGCs (also termed foam cells) that enhance calcified tissues surrounding arterial walls; an area that otherwise should not produce any mineralized tissues [13–17]. While the production of mineralized tissues from MNGCs in atherosclerosis leads to a pathological state, recently our group has questioned whether this situation might be advantageous around bone biomaterials. Thus, it is clear that a substantial amount of additional work is needed with respect to understanding macrophage and MNGCs function especially as it relates to bone biomaterials. It may be possible that MNGCs in certain situations leading to a pathological state (e.g. calcified tissues around arteries) might be therapeutic in others (bone biomaterials).

As part of an overview on the current knowledge regarding immune cells and bone biomaterials, this review article aims to: 1) Characterize and review the key basic science studies involving OsteoMacs that demonstrate their pivotal role in bone biology. 2) Provide background knowledge on monocytes and the great potential for these cells to differentiate into a variety of cell-types including M1 and M2 macrophages, MNGCs, FBGCs and osteoclasts. 3) Review the current literature on monocyte/macrophage studies with respect to bone biomaterials including bone grafts and dental/orthopedic implants. 4) Provide additional evidence from calcified atherosclerotic plaque that macrophages/MNGCs are potent inducers of mineralization by demonstrating that even in a pathological state, macrophages/MNGCs are the responsible cell-type contributing to calcification in arteries. 5) Demonstrate evidence from animal and human histological samples from our research center that MNGCs are routinely found around bone biomaterials in high numbers and commonly associated with the maintenance of high bone volume leading to the hypothesis that these cells may very well be one of the key players responsible for the maintenance of bone homeostasis.

2. OsteoMacs: biological basis and key roles in bone formation

The term ‘OsteoMacs’ was originally given by a group of basic researchers in Australia led by Allison Pettit. Original observations described in the mid 1980s sought to characterize the role of osteal macrophages in bone biology [18]. Hume et al. were one of the first to clearly demonstrate that periosteal and endosteal tissues contained a discrete population of resident tissue macrophages in line with traditional bone cell nomenclature [5,6]. OsteoMacs constitute approximately one sixth of all cells residing in bone marrow and display a stellate morphology allowing them to achieve extension coverage of bone surfaces suggesting that they may form a comprehensive communication network [6]. It is clear now that this subset of CD68+ cell-type is derived from a resident population of macrophages like macrophages found in other tissues [19–21]. More recent research has clearly confirmed that macrophages may subdivide and proliferate from resident tissues contrasting original theories expressing that these cells are derived from monocyte precursors from the blood-stream [22–25].

The general role of OsteoMacs has been described as immune surveillance cells in the bone microenvironment. A number of previous studies have demonstrated that this subset of macrophages are able to function as phagocytes [26,27], are capable of detecting bacterial products [28,29], and respond to antigens [27,30]. In vitro cell culture systems have further provided evidence by demonstrating how primary murine osteoblast cultures are able to respond to pathophysiological levels of lipopolysaccharide (LPS), characteristics of the M1 macrophage later discussed in this article [6]. These observations as well as others report the potential cross-

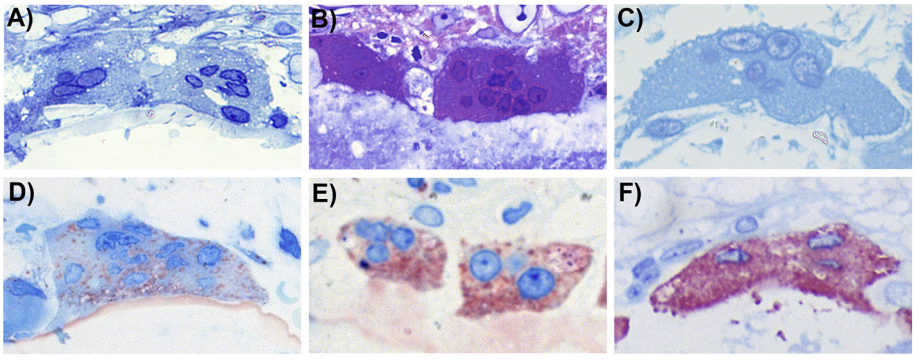

Fig. 1. MNGCs on bone substitute materials including (A, D) Bio-Oss® (HA), (B, E) Straumann® BoneCeramic (BCP), and (C, F) NanoBone® (HA-silica gel). LM (A–C) and TRAP histochemistry (D–F).