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Review article

Giant cells around bone biomaterials: Osteoclasts or multi-nucleated giant cells?

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ABSTRACT

Recently accumulating evidence has put into question the role of large multinucleated giant cells (MNGCs) around bone biomaterials. While cells derived from the monocyte/macrophage lineage are one of the first cell types in contact with implanted biomaterials, it was originally thought that specifically in bone tissues, all giant cells were bone-resorbing osteoclasts whereas foreign body giant cells (FBGCs) were found associated with a connective tissue foreign body reaction resulting in fibrous encapsulation and/or material rejection. Despite the great majority of bone grafting materials routinely found with large osteoclasts, a special subclass of bone biomaterials has more recently been found surrounded by large giant cells virtually incapable of resorbing bone grafts even years after their implantation. While original hypotheses believed that a 'foreign body reaction' may be taking place, histological data retrieved from human samples years after their implantation have put these original hypotheses into question by demonstrating better and more stable long-term bone volume around certain bone grafts. Exactly how or why this 'special' subclass of giant cells is capable of maintaining long-term bone volume, or methods to scientifically distinguish them from osteoclasts remains extremely poorly studied. The aim of this review article was to gather the current available literature on giant cell markers and differences in expression patterns between osteoclasts and MNGCs utilizing 19 specific markers including an array of CD-cell surface markers. Furthermore, the concept of now distinguishing between pro-inflammatory M1-MNGCs (previously referred to as FBGCs) as well as wound-healing M2-MNGCs is introduced and discussed.

Statement of Significance

This review article presents 19 specific cell-surface markers to distinguish between osteoclasts and MNGCs including an array of CD-cell surface markers. Furthermore, the concept of now distinguishing between pro-inflammatory M1-MNGCs (often previously referred to as FBGCs) as well as wound-healing M2-MNGCs is introduced and discussed. The proposed concepts and guidelines aims to guide the next wave of research facilitating the differentiation between osteoclast/MNGCs formation, as well as provides the basis for increasing our understanding of the exact function of MNGCs in bone tissue/biomaterial homeostasis.

Contents

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1. Introduction

The usage of implanted bone biomaterials in the fields of orthopedics, neurosurgery, and dental medicine has drastically risen over the past decade with an equally rapidly aging population [1]. The role of bone biomaterials has gradually evolved from a passive structural-support replacement graft towards complex scaffolding-systems exhibiting highly sophisticated surface morphologies and often carrying bioactive growth factors some of which possess osteoinductive properties [2,3]. While most research focused primarily on the response of mesenchymal cells (i.e., osteoblasts and fibroblasts) to bone biomaterials, only a small fraction of studies was dedicated to immune cells including monocytes, macrophages, osteoclasts, leukocytes and multinucleated giant cells (MNGCs) [4]. This discrepancy is difficult to understand given the fact that a large number of implanted bone biomaterials fail for completely unknown biological reasons [5].

Among the cells that first come in contact with an implanted biomaterial are monocyte/macrophage lineage cells. Macrophages play critical and distinct roles in immunity and bone tissue homeostasis and, importantly, are capable of polarizing towards 'M1' pro-inflammatory macrophages or towards 'M2' wound-healing macrophages [6,7]. Moreover, macrophages can fuse to larger multinucleated giant cells (MNGCs). Recent studies have shown that biomaterials can dictate the macrophage phenotype in such a way that they express wound healing and tissue regeneration M2 markers [8,9]. Likewise, MNGCs were also first characterized as 'bad' foreign body cells or an end-point conforming with material rejection around bone biomaterials [10–12], yet more recently, their phenotypes have also been shown implicated as possible contributors to tissue regeneration [13,14]. We therefore propose the concept of now distinguishing between pro-inflammatory M1-MNGCs (often previously referred to as FBGCs) as well as wound-healing M2-MNGCs. A better understanding of the biological response of macrophages to biomaterials and their possible fusion towards M1-MNGCs or M2-MNGCs denotes an important medical challenge to avoid or eliminate undesired immunological side effects [15].

An intriguing finding in recent years has been the discovery of macrophages and MNGCs located within atherosclerotic plaque [16–18]. Tissue sections retrieved from human arteries have shown that during the initial stages of atherosclerotic plaque formation tissue macrophages are typically expressing an M1 pro-inflammatory phenotype [16,17]. However, following an unknown period of time, for yet unknown reasons, these macrophages begin to polarize towards M2 tissue regenerative macrophages (termed 'foam cells'), often fusing into M2-MNGCs, and orchestrate the ectopic calcification of inflamed arteries [19]. And while cardiologists have characterized the calcification of arteries by MNGCs as pathological [19,20], recently our group has put into question the impact of such MNGCs found on certain classes of bone grafting particles or dental implants. In contrast to pathological states, they may rather present a quite favorable situation around bone biomaterials. Human tissue samples retrieved after bone augmentation procedures with a xenogeneic bone substitute material have consistently shown the presence of large MNGCs on the biomaterial surface [21]. While original hypotheses were led to believe that a 'foreign body reaction' may be taking place around such biomaterials, histological data from these human samples retrieved up to 80 months after their implantation have put this original hypothesis into question by demonstrating better and more stable long-term bone volume [22]. While the majority of giant cells around bone grafts are classical osteoclasts evidenced by their ability to resorb and replace bone grafts with native bone [23–25], certain bone biomaterials do neither lead to enhanced bone resorption nor provoke a foreign body reaction. However, exactly how this 'special' subclass of MNGCs is capable of maintaining long-term bone volume is presently unknown. Their characterization from osteoclasts, foreign body giant cells or atherosclerotic 'foam cells' remains completely unstudied. Therefore, it is clear that an understanding of the functional role of macrophages and MNGCs and their proper characterization is critical for the future development