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GIANT CELL FORMATION AND FUNCTION

William G. Brodbeck and **James M. Anderson**
Department of Pathology, Case Western Reserve University, Cleveland, OH 44106

Abstract

Purpose—This review is intended to provide insight into the current state of understanding regarding the molecular and cellular mechanisms underlying the formation and function of various types of multinucleated giant cells.

Recent Findings—Recent studies involving mainly osteoclasts and foreign body giant cells have revealed a number of common factors, e.g., vitronectin, an adhesion protein, dendritic cell-specific transmembrane protein (DC-STAMP), a fusion factor, and macrophage fusion receptor (MFR), that contribute to giant cell formation and function. Insight into common molecules, receptors, and mediators of the adhesion and fusion mechanisms of giant cell formation have been complicated by the wide diversity of species, models, and cell types utilized in these studies.

Summary—These recently identified factors together with the well-known osteoclast receptor, αvβ3, may serve as potential therapeutic targets for the modulation and inhibition of multinucleated giant cell formation and function. Further studies on intracellular and intercellular signaling mechanisms modulating multinucleated giant cell formation and function are necessary for the identification of therapeutic targets as well as a better understanding of giant cell biology.

Keywords

Multinucleated Giant Cell; Foreign Body Giant Cell; Macrophage; Osteoclast

INTRODUCTION

It is well-recognized that cells of the monocyte/macrophage lineage are capable of fusion to form multinucleated giant cells (MGCs). However, many aspects of their recognition, adhesion, fusion, and activation, in addition to specific intercellular and intracellular signaling pathways, remain unknown (**1,**2). Multinucleated giant cell phenotypes vary, depending on the local environment and the chemical and physical (size) nature of the agent to which the MGCs and their monocyte/macrophage precursors are responding.

This review focuses on recent efforts to develop a better understanding of the molecular and cellular biology of multinucleated giant cell formation and function. Recent studies on four different types of multinucleated giant cells are presented: giant cells from Mycobacterium-induced granulomas, giant cell tumors of bone, osteoclast formation and function, and foreign body giant cell formation and function. The review ends with a Conclusion section that identifies future issues and possible problems in our further elucidation of the molecular and cellular biology of multinucleated giant cells.

Corresponding Author: James M. Anderson, M.D., Ph.D., Case Western Reserve University, Department of Pathology, 2103 Cornell Road, WRB Rm. 5105, Cleveland, OH 44106, Telephone: 216-368-0279; Fax: 216-368-1546, e-mail: E-mail: jma6@case.edu.

GIANT CELLS FROM MYCOBACTERIUM-INDUCED GRANULOMAS

In studies utilizing an *in vitro* model of human tuberculous granulomas, Lay and co-workers have shown that high virulence mycobacterium, i.e., M. tuberculosis, induces large multinucleated giant cells with >15 nuclei per cell; whereas low virulence mycobacterium species, M. avium and M. smegmatis, have low numbers of nuclei per cell, <7. Of special note is that the high virulent mycobacterium species resulted in granulomas where the MGC phagocytic activity was absent, as opposed to the low virulence species that produced MGCs where phagocytic activity was present; all species demonstrated the presence of MGC NADPH oxidative activity (**3). MGCs with high numbers of nuclei per cell and produced by highly virulent mycobacteria are considered the final stage of formation and/or differentiation of MGCs as these cells are incapable of phagocytosis but still retain a strong antigen presentation capability. The authors consider that this model of human tuberculous granulomas enables the analysis of well-defined and well-differentiated granulomatous structures, consisting of all the specific cell types found within natural human granulomas, unlike those developed from other species.

This *in vitro* human granuloma model also has been used to identify the role of mycobacterial envelope glycolipids in granuloma formation (*4). In this model, mycobacterial pro-inflammatory phosphatidyl-*myo*-inositol mannosides and lipomannans and the anti-inflammatory lipoarabinomannan induce granuloma formation. However, only the pro-inflammatory glycolipids induce the fusion of granuloma macrophages into multinucleated giant cells and this process occurs through a Toll-Like Receptor 2-dependent, ADAM9- and β1 integrin mediated pathway. These findings relating substrate chemistry and the up-regulation of β1 in the macrophage differentiation and MGC fusion and formation processes are similar to those identified for FBGC development on foreign substrates, as described later.

GIANT CELL TUMORS OF BONE

Giant cell tumors of bone normally are found in meta-epiphyseal regions, forming after skeletal maturity (5). Following initial tumor formation, mononuclear histiocytic cells are recruited to the site of the tumor, and fuse to form MGCs. Receptor activator of nuclear factor κB ligand (RANKL) is expressed by neoplastic giant cell tumor stromal cells, promoting fusion with macrophage colony stimulating factor (M-CSF) acting as a cofactor.

Giant cell tumors are composed of mononuclear histiocytic cells, multinucleated giant cells, considered to belong to the monocytic-histiocytic system, and proliferating neoplastic tumor cells, also called giant cell tumor stroma cells (GCTSC), that do not belong to the monocytic-histiocytic system. Nishimura et al., have demonstrated that soluble factors from the giant cell tumor stromal cells can induce multinucleated giant cell formation from monocytes (6). These multinucleated giant cells have characteristic biomarkers suggestive of osteoclasts. Giant cell tumor stromal cells can facilitate the chemoattraction of mononuclear histiocytes as well as the formation of multinuclear giant cells. Gene expression of GCTSC suggests that these stromal cells are of early osteoblastic differentiation and also show differentiation features of mesenchymal stem cells.

OSTEOCLAST FORMATION AND function

Osteoclasts are multinucleated bone-resorbing cells that play a pivotal role in bone homeostasis and remodeling. Osteoclast precursors derive from bone marrow as early mononuclear macrophages, circulate in blood, and bind to the surface of bone. While the mechanism of recognition and target binding present on bone's surface is unknown, the integrin $\alpha_v\beta_3$ is the dominant osteoclast integrin and the marker of the osteoclast phenotype (7), which is initially absent on macrophage precursors, but progressively induced by RANKL. The $\alpha_v\beta_3$ integrin

recognizes the RGD (Arg-Gly-Asp) tripeptide sequence in several extracellular matrix macromolecules such as osteopontin, which is abundant in bone, as well as fibronectin, vitronectin, and fibrinogen. In addition to the high osteoclast expression of $\alpha_v\beta_3$, mammalian osteoclasts express $\alpha_2\beta_1$, a collagen-laminin receptor, and $\alpha_v\beta_1$, another vitronectin receptor.

Osteoclast formation is driven mainly by two cytokines, RANKL and M-CSF. RANKL is a member of the TNF superfamily and is considered the essential osteoclastogenic cytokine. It also is expressed on osteoblasts and their precursors and its production is enhanced by osteoclast-stimulating agents such as parathyroid hormone and TNF-α. Cell surface RANKL interacts with its receptor, RANK, on osteoclast progenitors. Osteoprotegerin (OPG) also is synthesized by osteoblasts and their precursors and is another member of the TNF superfamily. OPG recognizes RANKL and can thus function as a decoy receptor, competing with RANK. Overproduction of RANKL can lead to osteoporosis whereas overproduction of OPG can lead to osteopetrosis.

Inflammatory or periarticular osteolysis, a significant complication of rheumatoid arthritis, is a product of enhanced osteoclast recruitment and activation. As Teitelbaum has clearly expressed, the development of further understanding of the mechanisms by which the receptor activation of NF-κB ligand (RANKL), macrophage colony-stimulating factor (M-CSF) and tumor necrosis factor-α (TNF-α) modulate osteoclast behavior and can result in the identification of active and candidate therapeutic targets for the treatment of inflammatory osteolysis (8).

Osteoporosis results from the enhancement of the rate of bone loss by osteoclasts relative to the bone forming capacity of osteoblasts. Blockade of the $\alpha_v\beta_3$ integrin on osteoclasts offers a promising approach for anti-bone resorptive therapy (9). The β3 subunit is most commonly identified on osteoclasts, the placenta, and platelets. Although the platelet associates with a different α-integrin subunit, i.e., glycoprotein IIb, development of therapeutic modalities for osteoporosis must be specific and selective for the osteoclast integrin and not sufficiently broad to modulate the behavior of GPIIb β3 where platelet defects could lead to bleeding dyscrasias (7).

Yagi and co-workers, using a knock-out mouse model, have identified dendritic cell-specific transmembrane protein (DC-STAMP) as being required for the fusion of both osteoclasts and foreign body giant cells (10). Osteoclasts derived from the DC-STAMP knock-out mice were mononuclear, exhibited bone-resorbing activity, expressed osteoclast markers and cytoskeletal structure, but did not demonstrate cell fusion. Retroviral introduction of DC-STAMP in osteoclast precursors reestablished osteoclast multinucleation. Histological evaluation of Ivalon® (crosslinked polyvinyl alcohol) in DC-STAMP knock-out mice demonstrated abrogation of multinucleated foreign body giant cell formation. *In vitro* experiments using IL-3 and IL-4 treatment of macrophages from DC-STAMP knock-out mice demonstrated no FBGC formation. These studies clearly identify a common molecule necessary for the multinucleation, i.e., cell fusion, of both osteoclasts and foreign body giant cells. Vignery discussed the significance of identifying the ligand for DC-STAMP and determining if it is a surface protein expressed by macrophages or a soluble protein released by macrophages in a constitutive or regulated manner (11). Identification of a ligand for DC-STAMP has significant importance in developing therapeutic modalities related to osteoclasts, foreign body giant cells, and macrophage interactions with tumor cells.

FOREIGN BODY GIANT CELL FORMATION AND FUNCTION

Foreign body giant cells (FBGC) most commonly are observed at the tissue/material interface of implanted medical devices, prostheses, and biomaterials (**2). In this context, adherent macrophages and foreign body giant cells constitute the foreign body reaction (Figure 1).

FBGC also are seen in tissues where the size of foreign particulate is too large to permit macrophage phagocytosis. Generally, it is accepted that FBGC are generated by macrophage fusion and serve the same purpose as osteoclasts, degradation/resorption of the resorption of the underlying substrate. Table 1 identifies significant differences in factors believed to be important in the formation and function of osteoclasts and FBGC. Unlike osteoclasts, which adhere to bone, FBGC together with their macrophage precursors adhere to markedly different synthetic surfaces that display distinct differences in hydrophilic/hydrophobic character as well as chemical and physical properties (2).

The β1 and β2 integrin receptor families have been identified as necessary and sufficient mediators of adhesion during monocyte-to-macrophage development and IL-4-induced FBGC formation. Further identification of specific alpha partners to these beta integrins has identified the following expression profile for IL-4-induced FBGC: αMβ2, αXβ2, α5β1>αVβ1>α3β1, and α2β1 (*12). Complement components and fibrinogen have been identified as the early adhesion ligands to the β2 integrins and, at later times, vitronectin has been identified as the critical protein adhesion substrate for IL-4-induced FBGC formation (**13). This wide variation in integrin receptors and adhesion molecules is most probably the result of the wide and varied surface chemistries presented by synthetic substrates. Helming and Gordon have proposed a multistage process involving multiple target molecules for macrophage fusion induced by IL-4 alternative activation (*14). Studies with STAT6 knock-out mice have revealed IL-4-induced expression of E-cadherin and DC-STAMP in a STAT6-dependent manner. E-cadherin expression was critical for the formation of FBGC by IL-4. Monocyte/macrophage precursors from the STAT6 knock-out mice were not responsive to IL-4 in forming FBGC and also displayed a lack of phagocytosis (**15). Other studies with human monocyte/macrophage precursors demonstrated that FBGC formation exhibited features of phagocytosis with participation of components of the endoplasmic reticulum (16). The $P2X_7$ receptor, an ATP-gated ion channel belonging to the family of P2X purinergic receptors, has been implicated in the formation of all three types of MGC: FBGC, Langhans' giant cells, and osteoclasts. It has been suggested that $P2X_7$ is a common molecular step crucial for MGC formation (17). CD44 receptor expression is highly induced in macrophages at the onset of fusion. The intracellular domain of CD44 (CD44ICD) is cleaved in macrophages undergoing fusion and is localized in the nucleus of fusing macrophages in which it promotes the activation of NF-κB (18). Connexin 43 has been identified as playing a functional role in gap junction communication and the formation of osteoclast-like FBGC in response to implantation of nanoparticulate HA (hydroxyapatite) (**19). These studies have significant implications for hard tissue engineering and the reconstruction of bone defects.

In previous studies, T lymphocytes had been identified as a possible source of the IL-4 and IL-13 cytokines that induce macrophage fusion. Utilizing three different types of synthetic polymers, Rodriguez et al., demonstrated that FBGC formation and morphology were comparable between normal and T-cell-deficient mice. While IL-4 was not detected, IL-13 levels were comparable between normal and T-cell-deficient mice (20). *In vitro* cell culture studies using human monocytes/macrophages and lymphocytes demonstrated that pro-inflammatory cytokines such as IL-β, TNF-α, IL-6, IL-8, and MIP-1β were upregulated but no effect on anti-inflammatory IL-10 production was identified. Lymphocyte/macrophage/FBGC interactions through indirect (paracrine) signaling showed a significant effect in enhancing adherent macrophage/FBGC activation at early time points, whereas interactions via direct (juxtacrine) mechanisms dominated at later time points. Biomaterial surface chemistries differentially affected the observed responses with hydrophilic/neutral and hydrophilic/anionic surfaces evoking the highest levels of adherent cell activation relative to the other surfaces (21). Proteomic analysis and quantification of cytokines and chemokines from biomaterials surface-adherent human macrophages and FBGC showed significant differences in cytokine/chemokine profiles that were dependent on the polymer surface chemistry and properties.

While hydrophilic surfaces demonstrated a markedly reduced adherent cell density when compared to hydrophobic surfaces, the activation level of adherent cells on the hydrophilic surfaces was markedly increased over that on the hydrophobic surfaces. This study clearly demonstrated that material surface chemistry can differentially affect monocyte/macrophage/FBGC adhesion and cytokine/chemokine profiles derived from activated macrophages/FBGC adherent to biomaterial surfaces (**22,*23).

CONCLUSIONS

To date, studies on tuberculoid granulomas, osteoclasts, and foreign body giant cells have been complicated, and possibly confused, by the wide diversity of species and cell types that have been used in these studies. Knock-out systems have played a significant role in developing a further understanding of cell-cell fusion mechanisms but the question remains, “What other pathways and receptor-ligand interactions are compromised in these specific systems?” A clear example is the bleeding dyscrasias produced in β3 integrin knock-out systems utilized for osteoclast studies. In regard to foreign body giant cells and their significant *in vivo* interactions with medical devices, prostheses, and biomaterials, human and other mammalian blood monocytes, thioglycollate-elicited peritoneal macrophages, and alveolar macrophages have been utilized. Little is known regarding the similarities and differences of the phenotypes of these different monocytes/macrophages.

A better understanding of paracrine, juxtacrine, and endocrine interactions that facilitate and modulate multinucleated giant cell formation is necessary. The strengths and weaknesses of the use of specific species, models, and cell types, as they apply to the human condition, are necessary if mechanisms and signaling pathways are to be clearly delineated. In regard to the foreign body giant cell, the increasing utilization of biodegradable and non-biodegradable synthetic substrates in tissue engineering and regenerative medicine place special significance on developing a better understanding of FBGC formation and function, with the ultimate goal being the inhibition of FBGC formation and its potential adverse effects.

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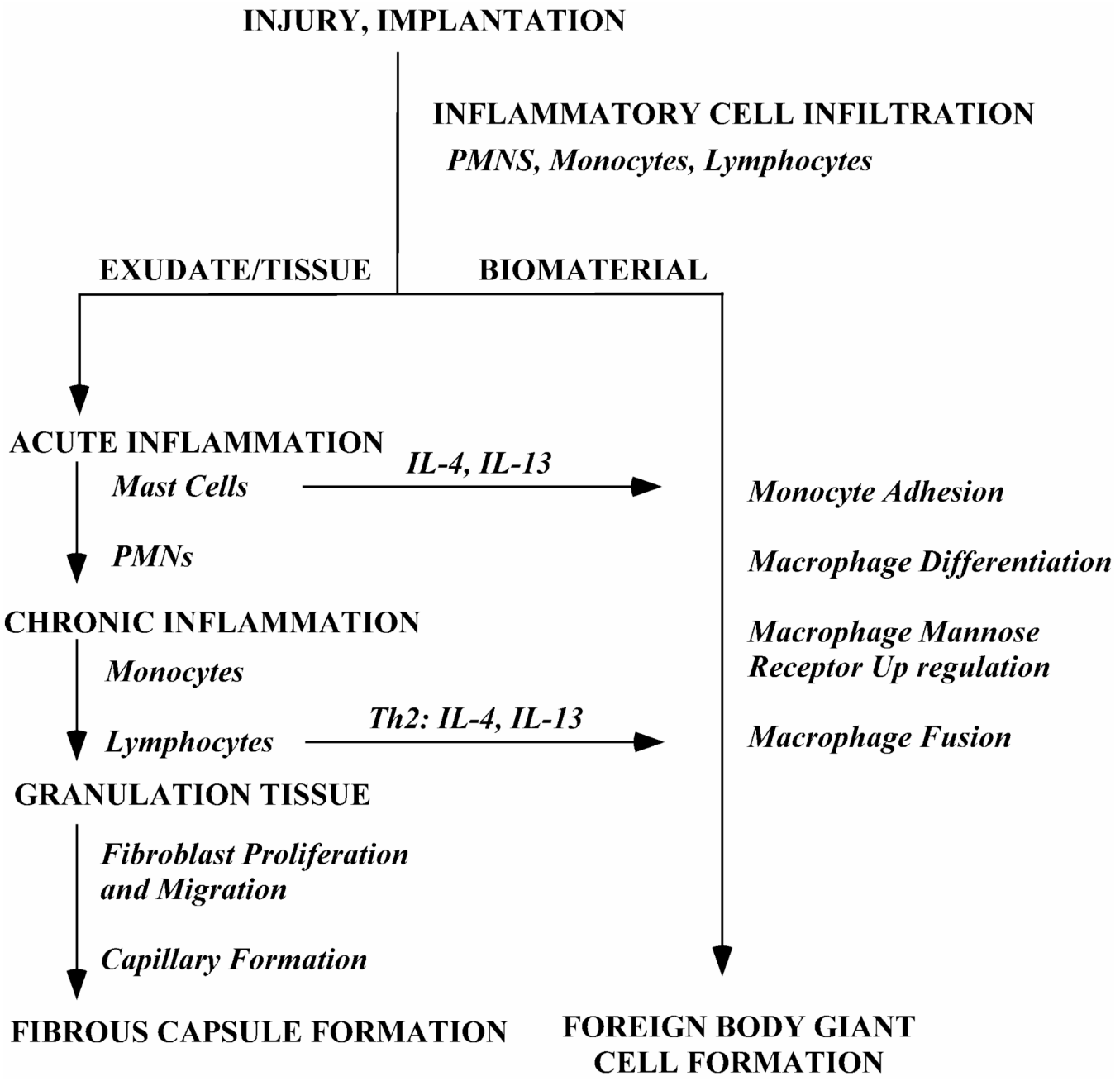

Figure 1.
Foreign body giant cell formation: Inflammatory and wound healing responses to implanted medical devices, prostheses, and biomaterials.

Table 1

Factors Contributing to the Adhesion and Fusion of Monocytes/Macrophagesin the Formation of Giant Cells

Contributing Factor	Osteoclasts	Foreign Body Giant Cells
Fusion (Adhesion) Substrate	Bone Dentin	Implanted biomaterials Hydrophobic/hydrophilic Neutral/Ionic
Surface (Adsorbed) Proteins	Osteopontin	Complement component (iC3b)
	Vitronectin	Vitronectin
	Fibrin(ogen)	Fibrin(ogen)
	Bone sialoprotein	
Adhesion Receptors,Integrins	$\alpha_V\beta_3$	$\alpha_M\beta_2$, $\alpha_X\beta_2$
CD47	$\alpha_5\beta_1$, $\alpha3\beta_1$	
		$\alpha_5\beta_1$, $\alpha_v\beta_1$
		CD44
		ICAM-1
Soluble Fusion Mediator	CCL-2	CCL-2
	RANKL	IL-4
	M-CSF	IL-13
	TNF-α	INF-γ
	IL-1	IL-3
		Con A
		PHA
Cell Surface Fusion Mediators (Receptors/Ligands)	DC-STAMP	DC-STAMP
MFR	MFR	
CD48	Mannose receptor (CD26)	
	$A_v\beta_3$	CD13 (aminopeptidase N)
	RANKL	Galectin-3
	E-Cadherin	E-Cadherin
	CD44, CD81, CD9	CD44, CD81, CD9
	Connexin 43	Connexin 43
		$P2X_7$ receptor
		Presenilin 2
Phenotypic Expression	Cathepsin K	Phagocytosis (frustrated)
	Acid	Acid
		Reactive oxygen intermediates
		Lymphocyte co-stimulators
		(HLA-DR, B7-2, B7-H1, CD98)CD44 (HCAM)