

Pathophysiology of Giant Cell Formation in Giant Cell Tumor and Lesions: A Review

Samar Khan

Assistant Professor, Dept of Oral and Maxillofacial Pathology and Microbiology,
College of Dentistry; Jazan University, Jazan (KSA).

ABSTRACT

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. Present article mainly focus on various factors such as e.g. GCP/F, GM-CSF, Meltrin, MIP-1 that contribute to giant cell formation and function. This review focuses on recent efforts to develop a better understanding of the molecular and cellular biology of multinucleated giant cell formation and function.

KEY WORDS: Multinucleated Giant Cell, Macrophage, Osteoclast. Macrophage inflammatory protein, Meltrin.

INTRODUCTION

A giant cell (GC) can be described as an unusually large, huge or gigantic cell; as a large multinucleate often phagocytic cell; cells with more than one nucleus. A multinucleate mass of cytoplasm that is not separated into cells. Giant cells were first described by **Virchow**. However according to other literature, **Lebert** is given credit for the first description. Synonyms of Giant cells include polykaryocytes and syncytium.⁽¹⁾

The osteoclast and syncytiotrophoblast of placenta are examples of normally found GC in the body. Skeletal and cardiac muscles may be regarded as multinucleated cells with specialized cytoplasm. Langhans, Touton, Foreign body giant cells, Reed-sternberg giant cells are some of the giant cells seen in relation to pathologic changes in the tissues.^(2,3)

A number of lesions that affect the jaws typically display multinucleated giant cells as one of their histopathological components. Till date very few to none articles have focused on pathogenesis involved in Giant cell lesions, thus this review article will further aid in understanding the pathogenesis of these lesions.

PATHOGENESIS

A number of lesions that affect the jaws typically display multinucleated giant cells (MGCs) as one of their histopathologic components.⁽²⁾Inspite of that the origin and the mechanism of formation of MGCs always unclear and matter of controversy. The various hypotheses proposed for pathogenesis regarding origin and formation of MGCs. of giant cells formation are discussed below.

1. Role of giant cell protein/ factors (GCP/F)

Evidence suggests that a heat labile protein, 60,000 MW, released from antigen stimulated lymphocytes promotes the formation of multinucleated giant cells from human monocyte precursors.

Several studies provide a basis for postulating that in humans, circulating monocyte might accumulate in granulomas at sites of cell mediated immune reactions by chemotactic migration in response to lymphocyte derived chemotactic factor for monocytes.^(3,4)

Macrophage migration inhibitory factor could act to retain monocytes at the granuloma site. Lymphocyte derived GCF fuses the accumulated monocytes and form multinucleated giant cells. Autoradiographic studies indicate that the lymphocyte derived giant cell protein (GCP) induces giant cells by fusion of non-replicating blood monocyte.⁽³⁾

2. Role of Osteoblasts/ Stromal Cells in Osteoclast Differentiation and Function:

Osteoclasts, the multinucleated giant cells that resorb bone develop from hematopoietic cells of the monocyte/macrophage lineage. Osteoblasts /stromal cells are involved in osteoclastogenesis through the mechanism involving cell to cell contact with osteoclast progenitor cells.⁽⁴⁾

A hypothesis proposed that osteoblasts /stromal cells express osteoclast differentiation factor (ODF) or 'stromal osteoclast forming activity' (SOFA) in response to various osteotropic factors such as 1-25-dihydroxy vitamin D3, PTH, and interleukin1. Osteoclast precursors of the monocyte-macrophage lineage recognize ODF /SOFA through cell to cell interaction with osteoblasts /stromal cells, and then differentiate into osteoclasts. Cell to cell contact between cells of the osteoblast lineage and hemopoietic cells is necessary for inducing differentiation of osteoclasts. Osteoblasts /stromal cells also play an essential role in the activation of osteoclast function.^(4,5,6)

3. **Role of Granulocyte –macrophage colony stimulating factor (GM-CSF) and macrophage colony stimulating factor (M-CSF)**

Granulocyte–macrophage colony stimulating factor (GM-CSF) and macrophage colony stimulating factor (M-CSF) stimulate the differentiation of human monocytes into 2 phenotypically distinct types of macrophages respectively. Various cytokines may modulate the differentiation of monocytes by CSFs. It is shown that CD 14 adherent human monocyte can differentiate into CD1⁺re1B⁺ dendritic cells (DC) by the combination of GM-CSF plus interleukin-4 (IL-4) and that they differentiate into tartrate resistant acid phosphatase (TRAP)-positive osteoclast-like multinucleated giant cells (MGC) by the combination of MCSF plus IL-4. However, the monocyte-derived DC are not terminally differentiated cells; they could still convert to macrophages in response to M-CSF.^(3,7)

Tumor necrosis factor- α (TNF- α) stimulated the terminal differentiation of the DC by downregulating the expression of the M-CSF receptor, c-fms mRNA, and aborting the potential to convert to macrophages. In contrast to IL-4, interferon-gamma (IFN- γ) had no demonstrable effect on the differentiation of monocytes. Rather, IFN- γ antagonized the effect of IL-4 and suppressed the DC and MGC formation induced by GM-CSF + IL-4 and M-CSF + IL-4, respectively.

Thus human monocytes are flexible in their differentiation potential and are precursors not only of macrophages but also of CD1⁺re1B⁺DC and TRAP positive MGC. Such a diverse pathway of monocyte differentiation may constitute one of the basic mechanisms of immune regulation. Monocyte differentiation into DC, macrophages, or MGC constitutes one of the basic mechanisms of immune regulation. It may depend on the stimuli and microenvironment; the cytokines profile during inflammation or infection would have a significant effect on these processes.^(3,5)

CD14⁺ human monocytes can differentiate into two phenotypically distinct types of macrophages. GM-CSF-induced macrophages were CD14⁺,c-fms^{low}, and M-CSF-induced macrophages were CD14⁺, c-fms^{high}. Differentiation pathways of monocytes induced by CSFs are modulated by IL-4; IL-4 stimulates the generation of CD1⁺ DC and TRAP⁺osteoclast-like MGC by cooperating with GM-CSF and M-CSF, respectively. IFN- γ suppressed the effect of IL-4. CD1⁺ DC generated from monocytes by GM-CSF + IL-4 still express c-fms, the M-CSF receptor, and can convert to macrophages by M-CSF but not by GM- CSF. After treatment with TNF- γ , the CD1⁺ DC lost the ability to convert to macrophages in response to M-CSF, because they did not express c-fms.⁽⁵⁾

4. **Role of Meltrin**

Meltrin α , β , and γ are members of a recently discovered family of proteins that contain disintegrin and metalloprotease domains and are related to fertilin, a protein involved in egg-sperm fusion. Evidences implicate the meltrin α in myoblast formation. Authors investigated the possibility that meltrins may also

play a role in the formation of macrophage derived giant cells and osteoclast. Using *in situ* RT-PCR, they have determined that murine mononuclear alveolar macrophages cultured under basal conditions express the transcript for meltrin-beta, but not for meltrin-alpha. However, meltrin-alpha mRNA appeared in mononuclear cells before cell fusion after treatment with 1,25-dihydroxyvitamin D₃ [1,25(OH)₂D₃], a potent inducer of giant cell and osteoclast formation.^(3,7,8,9)

Moreover, addition of meltrin-alpha antisense oligonucleotides to the cultures caused a 50% inhibition of giant cell formation. Similarly, meltrin-alpha antisense oligonucleotides inhibited by 70% the formation of multinucleated osteoclast-like cells expressing tartrate-resistant acid phosphatase (TRAP) in co-cultures of bone marrow cells and osteoblastic cells (2107) in the presence of 1,25(OH)₂D₃. Mononucleated TRAP-positive cells, induced by 1,25(OH)₂D₃ in the co-cultures, also expressed meltrin-alpha mRNA, but their number was not changed in the presence of meltrin-alpha antisense oligonucleotide. In contrast to mononuclear macrophages and osteoclast-like cells, murine bone marrow stroma and calvaria derived-cell lines (+/+ LDA.11 and 2107), primary cultures of calvaria cells, and primary cultures of bone marrow cells expressed both meltrin-alpha and -beta mRNA under basal conditions; whereas embryonic fibroblasts (NIH3T3) expressed only the meltrin-beta transcript.⁽⁷⁻⁹⁾

Upregulation of meltrin-alpha protein expression during cell fusion in alveolar macrophages and expression in osteoblastic cell lines were confirmed by Western blot analysis. These observations demonstrate that meltrins play a role in MGC and osteoclast formation from mononuclear precursors, as in the case with myotubes.^(3,7)

5. **Role of PTH and vitamin D3**

One of the major messenger pathways used to induce osteoclast formation is cAMP, with the most widely studied agonist for this pathway being para-thyroid hormone (PTH). The target cells of PTH in inducing osteoclast are osteoblast/ stromal cells but not osteoclast progenitors in the co-culture. Subclones of the human osteosarcoma cell line SaOS-2 were established to overexpress human PTH/PTH-related protein (PTHrP), PTH receptor 1(PTHR1) under heterologous promoter. Results indicate that the expression of PTHR1 in osteoblast is critical for PTH induced osteoclast formation in the co-culture.^(3,6,10)

6. **Role of Macrophage inflammatory protein-1(MIP-1)**

Chemokines, a family of the small cytokines are known to be chemotactic factors against various types of WBCs. Each chemokine has four conserved cystein residues and they can be classified into four types: C chemokines, CC chemokines, CXC chemokines and CXXXC chemokines; the classification depends on the number of aminoacids between the first and the second cystein residue. MIP-1, a member of CC

chemokines, has chemotactic activity against monocytes, lymphocytes, dendritic cells, eosinophils and natural killer cells. Thus, MIP-1 acts as the upregulator of osteoclastogenesis in bone. Very little is known about its mechanism of action.⁽³⁾

SUMMARY

Current article has briefly reviewed pathophysiological aspects of giant cell formation seen in various classic giant cell lesions and lesions occasionally showing giant cells. A number of lesions typically display multinucleated giant cells as one of their histopathological components. These newly acknowledged factors along with osteoclast receptor, Meltrin, M-CSF, 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.

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