

Giant Cell Formation- A Review

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Abstract: Though origin of formation of giant cells is still not clear, several studies discussed by various authors gave us a clear understanding that giant cells are formed by numerous mechanisms. These mechanisms involve fusion of monocyte lineage, myoblast fusion, macrophage fusion and also virus affected cell changes, along with anaplastic changes which gives rise to giant cells in various parts of the human body.

Keywords: Giant cell formation.

I. Introduction

"Giant" is the English word coined in 1297 commonly used for such beings which are very large when compared to normal.

According to The American Heritage Medical Dictionary Giant cell is defined as "an unusually large cell, especially a large multinucleated phagocytic cell."

A giant cell is a mass formed by the union of several distinct cells (usually macrophages) which undergo a defined set of intercellular interactions that ultimately result in a multinucleated cell with a single cytoplasmic compartment.⁵ C. Creighton suggested that giant cells can be found in both physiologic as well as pathologic states. Some of the physiologic giant cells are osteoclasts, odontoclasts, and cementoclasts.⁸ Giant cells are also associated in many pathologies when they are referred to as pathologic giant cells.

II. Origin Of Giant Cell

The origin of giant cells has never been established. Although their resemblance to osteoclasts is sometimes striking, seldom they are seen carrying out the ascribed normal resorptive function of such cells.¹

Geschicter and Copeland suggested giant cells might be derived from proliferating giant cells associated with resorption of deciduous tooth roots. Thus they suppose the lesion to be concerned with the transition from the deciduous to the permanent dentition. Such association of lesions is present only in few lesions even though tumors are quite common in youngsters. Such theory suggests the predominance of the giant cell lesions from anterior to the permanent molars.²

There has been considerable support for another theory of origin from endothelial cells of capillaries. There is some basis in fact for such an idea, the chief being the common occurrence of the giant cells within the vascular channels, suggesting that they arise here through fusion of endothelial cell. Another theory suggests multinucleated giant cells apparently result from fusion of the proliferating mononuclear cells.² Several investigations have demonstrated that giant cell formation is the result of fusion between monocytes. This type of fusion potential is seen as an unique feature in adult mammalian tissues, with an exception of myoblasts in injured muscle.³

Arnold e. Postlethwaite et al also suggested that multinucleated giant cells may arise from the fusion of non replicating monocytes or from the mitotic and amitotic division of monocyte nuclei in the absence of cellular division. It is thought that cellular immune mechanisms play a direct role. His studies suggested that a heat-labile protein of approximately 60,000 molecular weight are released from antigen- or mitogen-stimulated lymphocytes promotes the formation of multinucleated giant cells from human monocyte precursors.⁴ Barbara k. Jackson et al finally suggested that the morphology of the multinucleated giant cells formed in vitro after exposure of blood monocytes to the lymphocyte-derived factor is generally different from that of the classic giant cells of the Langhans' type found in vivo at sites of delayed hypersensitivity reactions.⁴

In a study conducted by Johnathan L. Barteo on mouse macrophages treated with lipopolysaccharide (LPS), a Gram negative bacterial endotoxin, or lipoteichoic acid (LTA), a Gram positive bacterial endotoxin. It was found that LPS and LTA both elicit the release of Tumor Necrosis Factor Alpha (TNF- α) from macrophages, which induced cellular fusion. Hence his results show that a macrophage cell line provides a robust and reliable model for MGC formation.^{5,6,7}

III. General Mechanism Of Cell Membrane Fusion:

The current concept regarding the cell membrane according to Singer and Nicolson (1972) is that it consists of a lipid bilayer in which proteins float on the outer surface in varying degrees. Many of these proteins extend right through the bilayer appearing on both the inner and outer surfaces and these proteins are known as integral proteins. Poste and Allison et al in 1975 suggested that there are alterations in the position or properties of these integral proteins by environmental agents, which leads to changes in the internal surface of the cell and allows the cell to recognize the environmental stimuli.³

Lawson et al in 1977 suggested that the fusion of the surface membrane is always preceded by the cell surface alteration. His studies showed that during membrane fusion of cells, the fusion takes place between areas of cell membrane from where surface proteins are absent.^{3,8}

IV. Factors Affecting Giant Cell Formation:

Merry Jo Oursler in her study showed that RANKL signaling is essential for osteoclast fusion and several cellular components that are involved in fusion act by promoting this pathway.

Later Kara et al supported the above statement saying that the adenosine A1 receptor is a G protein coupled receptor implicated in osteoclast differentiation which is required for RANKL signaling leading to osteoclast fusion.^{6,9}

V. Cell Membrane Fusion Various Theories Of Giant Cell Formation

1. Multiple Nuclear Division Without Cytokinesis

According to Harris (1968) nuclear division in a polykaryon is normally followed by the formation of a single mitotic spindle, leading to the production of a single hyperdiploid nuclei.

He also stated that formation of giant cells (e.g. tumor giant cells) occurs by the nucleus of the dividing cell, while the body of the cell fails to divide. These giant cells are not derived from the macrophages but from the cells of the tumor either connective tissue or epithelial in nature.¹⁰

2. Macrophages Fusion :

Gorden and Cohen in 1970 suggested that macrophages can fuse with other macrophages to form a giant cell in vivo. Three suggestions have been put forward to account for macrophage fusion in vivo.¹⁰

A. Fusion Mediated By The Immune System

Macrophage polykaryons are commonly found in areas containing poorly removable foreign material. Frequently the foreign body is antigenic (fungi, tuberculosis, etc). Even when the foreign material itself has no antigenicity (eg, glass) it is possible that inflammatory process itself produces antigens. It has been stated that immune system is probably responsible for macrophage fusion. It has been suggested phagocytosing macrophage fuse under the influence of lymphokines and the membrane changes associated phagocytosis may facilitate the adherence and fusion of macrophages initiating the formation of the giant cell.¹⁰

B. Fusion Resulting From The Recognition Of An Abnormal Macrophage Surface By Young Macrophages.

Mariano and Spector (1974) showed that by enclosing a population of macrophages in diffusion chambers; invitro giant cell formation was prevented. On leaving the chambers open, they found that the fresh incoming macrophages fused with those already inside the chamber to form giant cells. It was seen that being enclosed within the chamber, the macrophages underwent mitosis, which revealed many chromosomal abnormalities. These chromosomal abnormalities lead to the formation of an abnormal cell surface on aging population which is recognized by the fresh incoming cells leading to fusion.¹⁰ Contradicting Mariano and Spector's hypothesis later in the year 1977 Chambers tested this hypothesis by exposing macrophages cultured in inflammatory exudates to fresh macrophages. It was observed that no fusion took place between two populations.

C. Fusion As A Result Of Endocytic Activity

Chambers (1977) suggested that if the foreign material gets attached to the surface of the macrophages, it meets the phagosomic margins of the other cell. Attachment of any variety of substances (foreign material) to the macrophage surface is followed by formation of endosome margins, which then approach each other and fuse to complete the endosome formation. It was seen fusion occurred in between the margins of the two cells.¹⁰

3. Formation Of Giant Cells Induced By Viruses:

Hernandez et al (1986) suggested that fusion may be caused by large numbers of inactivated viruses or by much small infective virus. With the inactivated virus, the viral envelope attaches and leads to a reduction in the cell coat thickness. When the virus is in contact with more than one cell, it results in cell fusion. Antigens from the virus get incorporated into the polykaryon membrane, indicating that the fusion results from the viral envelope leading to a "bridge" between the two cells, which enlarges into complete cell fusion.^{9,10} The mechanism by which enveloped viruses enter cells has very well defined by Hernandez et al under molecular basis. It says binding and fusion of viruses with host cells is mediated by viral proteins and host cell surface molecules that are used as viral receptors. Virus and host cell plasma membrane binding is mediated by a 'receptor±ligand' type of interaction.

- For instance, the human immunodeficiency virus (HIV), which causes AIDS, binds CD4 on T lymphocytes and macrophages;
- Rhinoviruses binds to ICAM-1;
- Haemagglutinin influenza virus binds specific sialic acid residues.

The binding of viruses to host cells is mediated by a viral membrane protein which acts as a 'ligand' for the host cell receptor. Such ligands include the HIVgp120 surface protein which binds CD4 and the HA1 of influenza virus which binds sialic acid residues.^{6,7,9}

Live viruses can also cause fusion in the same way at higher levels, but when the proportion of the virus to the cell is low it must penetrate the cell and lead to a fusion following the appearance of virally coded proteins on the cell surface. The infected cell thus has a surface modified by viral proteins and this leads to fusion with the adjacent uninfected cell. Eg, Warthin-Finkeldey multinucleate cells are seen in measles.^{6,7,9}

VI. Classification Of Giant Cells

I. According To Boyd (1995)¹¹

A. Tumor giant cells

- ❖ Giant cell in osteogenic sarcoma
- ❖ Giant cell in rhabdomyosarcoma
- ❖ Giant cell in primary CA of liver

B. Foreign body giant cell

- ❖ Langhans giant cell
- ❖ Giant cell in sarcoidosis
- ❖ Giant cell in leprosy

C. Miscellaneous

- ❖ Aschoff cell
- ❖ Reed stern berg cell
- ❖

II. Chattopadhyay (1995)¹² has classified giant cells under the following headings

1. Damaged striated muscle fibres.

- a. Regenerating sarcolemmal cells in damaged voluntary muscle.
- b. Aschoff giant cells in heart muscle (fused myocardial macrophages).

2. Fused fibroblasts (as in giant cell fibroma)

3. The osteoclast.

4. Tumor giant cells.

- a. Reed-stern berg cells in Hodgkin's lymphomas.
- b. Giant cells in central giant cell granuloma, poorly differentiated astrocytoma.
- c. Giant cells in other tumors e.g. Carcinoma, malignant fibrous histiocytoma.

5. Fused cells due to viral infections.

- a. Epithelial giant cells as in HSV infection.
- b. Connective tissue cells as in Measles (Warthin Finkelday cells).

6. Fused macrophages

- a. Due to reaction to foreign bodies (exogenous or endogenous materials) e.g. foreign body giant cell with scattered nuclei.

- D. Due to reaction to organism as in tuberculosis (Langhan's giant cell) and fungal infections.
- E. Touton giant cells of xanthoma

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