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Macrophage Distinct Process: Efferocytosis in Oral Cancer

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Abstract

Macrophages and neutrophils are the first defendants to invading pathogens and play a part in host defense against intracellular pathogens. Macrophages come into sight to play a major role in efferocytosis, phagocytosis of dead cells that contain bacterial content. Macrophages are distributed in tissue everywhere in the body, principally not the only digest and destroy invading pathogens, but are associated with clearing dead and dying host cells. The efferocytosis is explicated as the process of engulfing apoptotic cells and has long been depreciating for its role in the condemnation of inflammation**.**

Keywords: Macrophages, Neutrophils, Efferocytosis, Phagocytosis.

Introduction

Efferocytosis: The word obtained from efferre, Latin for "to take to the grave" or "to bury." In cell biology, it is the procedure by which dying/dead cells (e.g., necrotic or apoptotic cells) are abolished by phagocytic cells. It can be defined as a phenomenon of "burying of dead cells."[1] The term efferocytosis, particular for the aforementioned phenomenon.[1, 2]

Cellular cannibalism: It described as a large cell indicate a slightly smaller one within its cytoplasm. It has been reported in various cancers like breast cancer, lung cancer, gastric cancer, oral squamous cell carcinoma. Cellular cannibalism has been well correlated with anaplasia, aggressiveness and grading of the tumor, and metastatic potential.[3]

Efferocytosis-how it differs from cellular cannibalism

During the procedure of efferocytosis, the cell membrane of phagocytic cells changes and engulfs the apoptotic cell, developing a large fluid-filled vesicle containing the dead cell. This ingested vesicle is known as an efferosome (in similar to the term phagosome). This process is an analogy to the process of macropinocytosis. In apoptosis, efferocytosis play the active role of removing the dead or decayed cells before their membrane integrity is breached and their contents escape into the surrounding tissue. This inhibits the exposure of tissues to the toxic and caustic enzymes, oxidants, and other intracellular components such as caspases and proteases and which would diversely affect the integrity of the tissue[4] To differentiate themselves from the living cells, apoptotic cells carry

particular 'devour me' signals such as the presence of phosphatidylserine (PS) (developing from phospholipid flip-flop) or calreticulin on the outer surface of the cell membrane.[5]

Efferocytosis triggers certain downstream signal transduction pathways within the cell that result in anti-protease, anti-inflammatory, and growth promoting effects. Contrariwise, defective efferocytosis has been linked to tissue damage and autoimmune diseases. It provokes the host cell to produce mediators like vascular endothelial growth factors and hepatocyte, which are assumed to enhance replacement of the dead cells. The defective process of efferocytosis has been conspicuous in diseases like a chronic obstructive pulmonary disease, asthma, bronchiectasis, cystic fibrosis, rheumatoid arthritis, systemic lupus erythematosus, (SLE), glomerulonephritis.[6]

The function of macrophages

Macrophages function principally as phagocytes during innate immune activity but accomplish various actions in homeostasis and disease. During infection, recognition of pathogen-associated molecular patterns (PAMPs) by macrophages leads to the formation of chemokines and cytokines, promoting the enrollment of other cells and precipitating an immune response. By degenerating pathogen-derived antigens and introducing them to T cells, macrophages can perpetuate adaptive immunity.[5] Moreover, by degrading and degrading bacteria, macrophages decontaminate tissue, resolve inflammation, and inhibits further stimulation of the immune system.

In accretion to their roles in the immune response to infection, macrophages perform a second, conceivably more important function. They are the cell type commonly responsible for efferocytosis, the process of engulfing and exterminating apoptotic cells. Apoptosis, or programmed cell death, is compulsory for the production of multicellular organisms, and even in adults, thousands of cells die and are eliminated every second. [6, 7]

Efferocytosis-predictor of oral cancer

Apoptosis in OSCC is a very customary event that can easily be observed on routine histopathological examination. Hence, efferocytosis in oral cancer is quite an imaginable phenomenon. It is well hypothesized in the literature that epithelial cells can also accomplish efferocytosis. Sarode GS examined oral squamous cell carcinoma slides for histopathological corroboration of efferocytosis by tumor (epithelial) cells. On careful histopathological examination, they observed that tumor cells of oral cancer envelop the apoptotic cancer cells. The internalized apoptotic cells manifested typical features of programmed cell death containing densely concentrated eosinophilic cytoplasm, pyknotic nuclei or condensed chromatin and disappearance of intercellular bridges [Figure 1a and b]. These internalized apoptotic cells gave the perception of being surrounded by a clear halo appearing efferosome production by the inundating or host tumor cell. The nuclei of these host cells observed to be pushed towards periphery representing it in a crescent or semilunar shape. There was no documentation of intercellular bridges between host tumor cell and internalized apoptotic cell. [Figure 1a and b]. Both complete and partial and complete engulfment was observed in oral squamous cell carcinoma. Moreover, cannibalism could also be freckled along with efferocytosis. [Figure 2]. [7, 8]

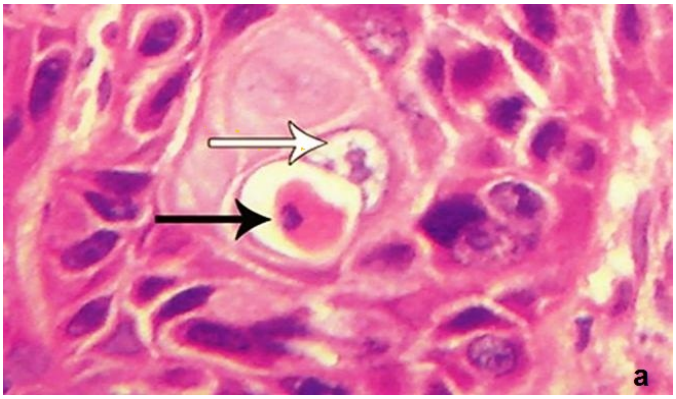

Figure 1: (a) Photomicrograph demonstrating complete engulfment of apoptotic cell (black arrow) by oral squamous cell carcinoma tumor cell (white arrow) (H&E stain, ×400),

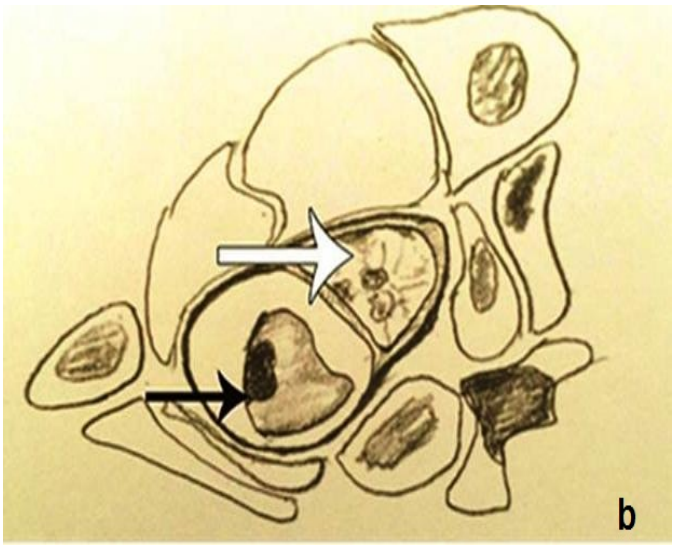

FIGURE 1 (b): Hand drawn illustration of the photomicrograph of 1a showing apoptotic cell (black arrow) and host cell (white arrow)

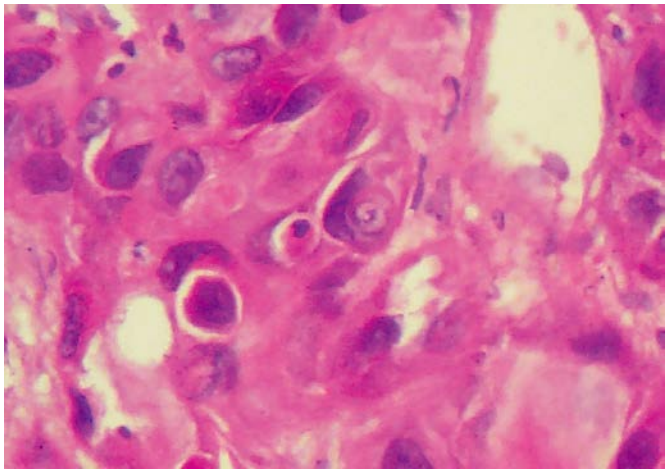

Figure 2: Photomicrograph demonstrating cellular cannibalism efferocytosis and together. The nuclei of engulfing cell represented the characteristic semilunar- (H&E stain,x400)

Mechanism of efferocytosis

Efferocytosis is deliberately regulated at multiple levels. At first, cells undergoing apoptosis produce soluble factors that captivate the host cell (epithelial cells, macrophages or fibroblasts) to the site of death, indicating to as 'find me' signals, which implicate the chemokines CXCL1, CXCL14, CCL2, CCL6–8, and CCL11.[8]

The apoptotic cell also features its outer leaflet with the 'devour me' signal, permitting the host cells to perceived and bind to the apoptotic cell. PS exhibited on the outer layer of the plasma membrane of an apoptotic cell is a distinctive feature of programmed cell death and is the most commonly recognized 'devour me' signal. Healthy cells vigorously retain PS on the inner layer of the plasma membrane. In disparity, at the onset of apoptosis, PS assembles on the outer leaflet, pointing the apoptotic cell for engulfment.[9] In reaction to the 'find me' signals, the deluging host cells upregulate cell surface receptors and bridging molecules. These bridging molecules synchronously bind to PS and surface receptors of host cell. Host cells use various cell surface receptors to directly identify PS and many other receptors that attach to bridging molecules to secondarily bind PS on the apoptotic cell to the host cell. Once dissipated, the cell is processed by degradation of lysosome. [10]

In supplement to engulfment and degradation of the apoptotic cell, efferocytosis stimulates expression and production of immune suppressive cytokines such as IL-10, IL-13, IL-4 and transforming growth factor-beta 1 and suppression of pro-inflammatory cytokines (IL-12 and interferon gamma). This stimulates tissue repair and immune tolerance. [11]

Beyond the important function of efferocytosis in tissue homeostasis. Recent studies conclude that efferocytosis may reinforce a more malignant tumor microenvironment, in part because of the cytokine signature related with the process.[12] In addition, many ligands and receptors that facilitate the process of efferocytosis are overexpressed in cancer suggesting a certain role in tumorigenesis.[13, 14]

Conclusion

Efferocytosis has been proved to be a significant morphological parameter and has been described in a diversity of cancers. It has been well correlated with tumor aggressiveness, grading, and metastatic potential. Hence it is recommended to examine each cancer specimen for identification of efferocytosis to validate its role as a morphological predictor. Literature scrutinizes fetched up sparse studies concerning efferocytosis and oral squamous cell carcinoma (OSCC) and therefore warrant a call for forthcoming involved researchers to justify the role of efferocytosis as a prognosticator of OSCC.

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