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Cannibalism- Another warfare mechanism of tumor cells

[1]Siva Kumar R, Assistant Professor, Department of Oral Pathology & Microbiology, KUHS, Kerala, India

[2]Jayashree, Post graduate, Department of Oral Pathology & Microbiology, KUHS, Kerala, India

[3]Heera R, Professor& HOD, Department of Oral Pathology & Microbiology, KUHS, Kerala, India

[3]Geethu, Post graduate, Department of Oral Pathology & Microbiology, KUHS, Kerala, India

[3]Sruthy, Post graduate, Department of Oral Pathology & Microbiology, KUHS, Kerala, India

Corresponding Author: Jayashree S, Post Graduate, GDC Trivandrum, Kerala, India.

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Abstract

Cellular cannibalism is defined as the ability of a cell to engulf or phagocytose another cell of its own type or any other. It was first described by Leyden in 1904, who coined those cells as "bird's-eye cells". Cellular cannibalism differs from phagocytosis, entosis, emperipolesis and autophagy; though it may mimic these phenomena. In 1981 Steinhaus described the cell in cell phenomenon in tumor cells. It has been described in various cancers like bladder cancer, breast cancer, lung cancer, gastric cancer, oral squamous cell carcinoma. Tumor cells resort to cannibalism to fulfil their nutritional requirements and to escape immune attack. Cellular cannibalism has been well correlated with anaplasia, tumor aggressiveness, grading and metastatic potential. Present review elaborates on mechanism, types of cannibalism and its significance in various pathologies with an emphasis on oral carcinoma.

Keywords: Cannibalism, Tumor cannibalism, Oral squamous cell carcinoma, Giant cell lesions, Phagocytosis.

Introduction

The word "cannibalism" springs from Spanish word "caníbal" in regard to alleged cannibalism among Caribs. In Greek, it's mentioned as anthropophagy, which refers to custom or act of humans eating other human[1,2]. In 1904, Leyden described cannibalism in cytopathology and histopathology and used the term "bird's-eye cells" or "signet-ring cells" for cannibalized cells[3]. Cellular cannibalism (CC) is defined as an outsized cell enclosing a rather smaller one within its cytoplasm.[4]Cannibalistic cells (CCs) were initially observed in cytological smears where the cell that had ingested another cell consisted of a vacuole containing the ingested cell and this vacuole pushed the nucleus to the periphery of the cell. This unusual property of tumor cells gets fortified over survival at low nutrient adverse conditions.[2]

Types

Basic types of cannibalism are as follows.

Survival cannibalism: Human consumes other humans flesh for survival in emergency situations like starvation. It's known as survival cannibalism. 1846-47 Donner Party a group of Yank pioneers led by George Donner and James F. Reed (referred to as the Donner Party), migrated to California in a wagon train from the Midwest. The journey to California usually took 4 to 6 months, but after their attempt to take a new short route, they spent five months in the winter of 1846-47 snowbound in Sierra Nevada, resorting to cannibalism and culminating in death. Among 87 men, women and children, 46 survived.[5]

Endocannibalism: The consumption of human flesh from a member of one's close social group. They followed this as a cultural practice. [6]

Exocannibalism: The consumption of flesh outside one's close group. As an example, eating one's enemy. Reports of this practice suggests headhunting and thus the display of skulls as war trophies[7]. It has been associated with being a means of imbibing valued qualities of the victim or as an act of final violence against the deceased in the case of sociopathy, as well as a symbolic expression of the domination of an enemy in warfare. Such practices have been documented in cultures including the Aztecs from Mexico, the Carib and the Tupinambá from South America.

Mortuary cannibalism: takes place as part of funeral rites and can be practiced as a form of affection, or as an act of renewal and reproduction[8].

Warfare cannibalism: is the consumption of enemies, which can be in part honoring brave opponents or exhibiting power over the defeated.

Types of cellular cannibalism

i) Self-cannibalism (macro autophagy): is a well-regulated process of cell repair as well as of molecule and organelle recycling that allows the cells to survive[9].

ii) Xeno cannibalism: Recent reports have shown tumor cell engulfing other cells (xeno-cannibalism) as well, such as neutrophils, lymphocytes and erythrocytes[10].

Peculiarities of cannibalism: The engulfed cell still remains alive when internalized, but the method implies its death. This is how cannibalism is differentiated (table 1) from several other kinds of cell engulfment. [4]

Cellular cannibalism fundamentally differs from,

- Phagocytosis
- Entosis
- Emperipolesis
- Autophagy
- Efferocytosis

Though it mimic these phenomenon

Phagocytosis: Phagocytosis is characterized by a really expensive and dramatic process through which macrophages embrace, surround, and engulf the external body through long arms referred to as pseudopods.[11]

Entosis: Entosis is a homogeneous (cells of same type) cell-in-cell invasion while cannibalism can be either homogeneous or heterogeneous cell-in-cell structures. The process of entosis is different from cannibalism in that entosis is a live cell invasion while cannibalism has no selectivity for dead cells or live cells. In entosis, live epithelial cells or tumor cells detach from extracellular matrix then invade their neighbour cells. Entosis depends on conjugations or adherens junctions and needs Rho and Rho-associated protein kinase (ROCK) activities for internalization, suggesting that entosis is an active process and requires actin polymerization[12].

Emperipoleosis

Emperipoleosis is a heterogenous (cells of different type) cell-in-cell invasion in which engulfed cells are hematopoietic in origin. The internalized cells remain within the outer cell temporarily and are not destroyed.[4]

Efferocytosis

The recognition and elimination of apoptotic cells by tissue macrophages and non-professional phagocytes (epithelial cells, endothelial cells, fibroblast and neutrophils) referred to as efferocytosis. It is different from other kinds of cell-in-cell phenomena both cytologically and biologically.[15]

Table I. Cannibalism and Other Forms of Cell Engulfment

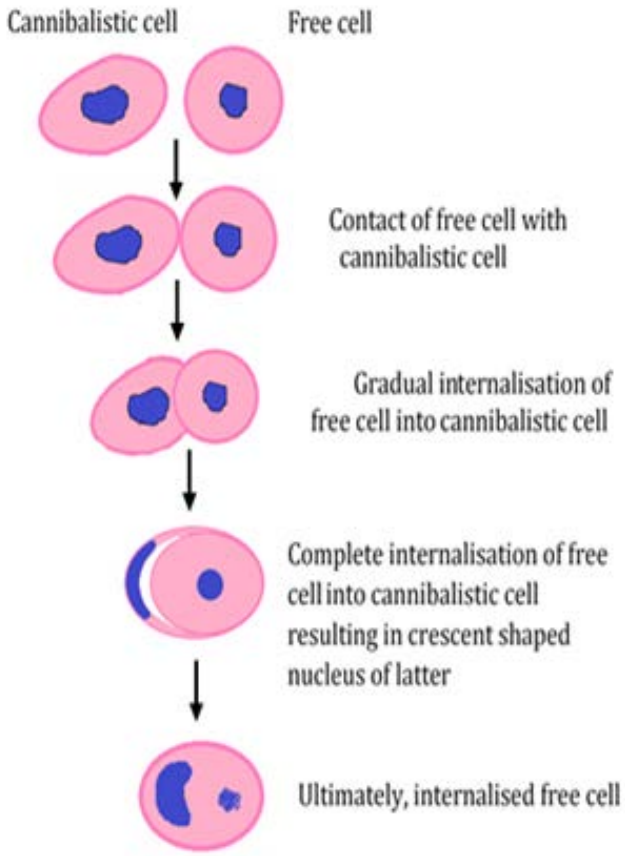
Type of cell eating	*Classical feature*
Cannibalism	Cell within cell causing death of cell
Emperipoleosis	Cells not destroyed
Phagocytosis	Pseudopods or surface ruffles
Autophagy	Membraned autophagic vacuoles (named autophagosomes)
Benign multinucleated cells	Result of chemotherapy/radiotherapy
Entosis	Cell-in-cell invasion process

Step by step process

Brouwer et al proposed the successive steps /process of cannibalism. [7, 8]

1. In the first step, cannibalistic cells come in close proximity with the free cell.
2. Next step, cannibalistic cell engulfs the cytoplasm of free cell.
3. After engulfment of the cytoplasm of free cell, the nucleus remains the same. But the nucleus of the cannibalistic cell changes to semi lunar shape.
4. Finally the free cell completely dies off and its nucleus disintegrates.

Exact mechanism by which tumor cells end up feeding on their sibling tumor cells remains ambiguous. However, recent literature suggests that tumor cell cannibalism may be a favorable event in malignancy and is assumed to be accountable for tumor resistance against specific immune reaction. Also, tumor cells may use this process as a source of nourishment in setting of deficient nutrient supply and unreceptive tumor microenvironment.[1, 2, 4]



Grading of cannibalism

The following five parameters are used to assess grading of cannibalism:

- Cellularity of cannibalism
- Diameter of cannibalistic cell
- Chromatin pattern
- Background(necrosis, isomorphic erythrocytes, and dysmorphic erythrocytes)
- Vimentin reactivity

Cellularity of cannibalism has been semi quantitatively assessed as follows:

(1+) <5 cells

(2+) 5–20 cells

(3+) >20 cells in each preparation

Diameter of cannibalistic cells have been analyzed using an image analysis system. Chromatin pattern is evaluated as heterochromatin pattern or euchromatin pattern.[4]

Tumor cannibalism

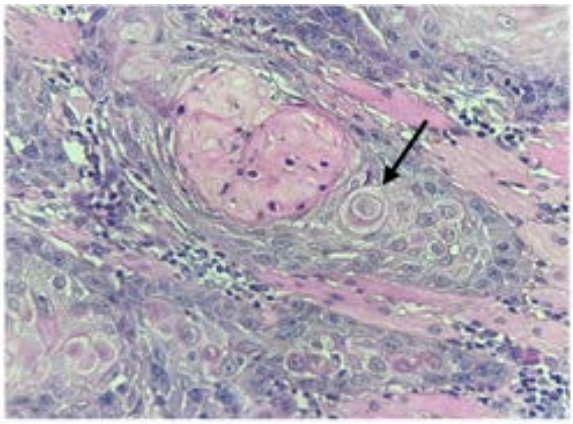


Fig 1: figure showing cannibalistic cell in H &E stained section

In 1981 Steinhaus described the cell in cell phenomenon in tumor cells (Fig 1). Cellular cannibalism has been described previously in breast carcinoma, giant cell carcinoma of lung, gall bladder carcinoma, endometrial stromal carcinoma, malignant thymoma, melanoma etc. and is correlated well with the aggressiveness, degree of anaplasia, invasiveness and metastatic potential of malignancy.[10]

Cannibalism in Oral Squamous Cell Carcinoma (OSCC)

Cannibalism is often considered as tumor defense against the host immune mechanisms and may be spotted on hematoxylin/eosin-stained sections of OSCC[16]. Cells with cannibalistic behavior are detected in tumors of varied histology, and their presence has been related to poor prognosis and aggressive nature.

Cannibalism is recognized as a phenomenon commonly employed by unicellular and higher organisms, even at single-cell level, as a survival option. It's not clear whether cells, ready to feed through other cells, are present in a normal physiologic state of body, but cannibal cells were identified in malignant tumors up to a century ago.[17]

Studies show malignant cannibal cells prey on adjacent tumor cells and leukocytes to drive their metabolic activities. This is often mediated by cathepsin B, lysozyme, and other lytic enzymes, mimics phagocytosis, and may be a process of nonselective cell eating.[10]

Factors involved in cancer cannibalism:

The transformation of a neoplastic cell into a cannibalistic cell is a process involving numerous sequential events. Initial events could be associated with genetic expression of proteins required for the execution of cellular cannibalism. Molecules that are involved in this process are CD68, lysozyme, caveolin-1, actin, ezrin, cathepsin B, 9 transmembrane segment (TM9SF4), and vimentin. Later, genetic expression is manifested in the form of engulfment and digestion of adjacent cancer cells that are detectable on routine histopathology.[19]

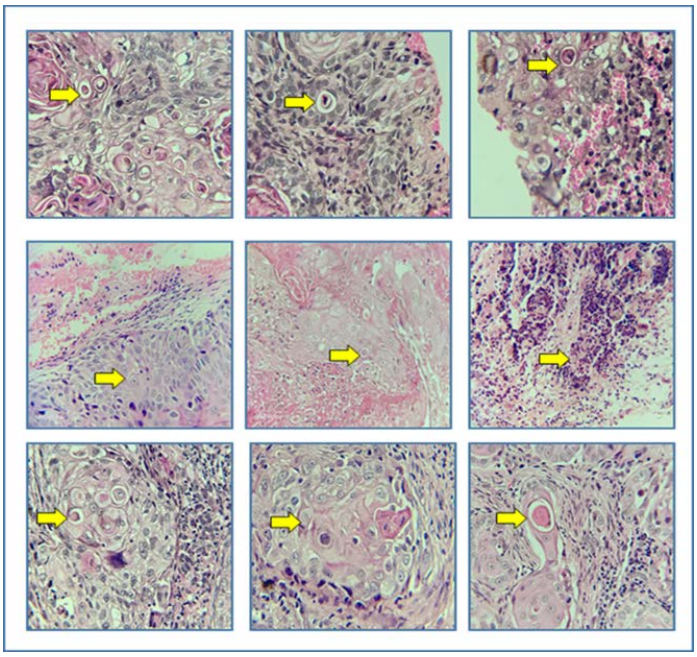


Fig.2: showing cannibalistic cell in various cases of OSCC (H&E .10x magnification)

Genetic and molecular mechanism

The development of OSCC is a multistage process that involves the progressive transition of the normal oral epithelium through epithelial dysplasia to invasive carcinomas. These steps are characterized by the sequential accumulation of genetic alterations in proto-oncogenes, tumor suppressor genes (TSGs), and

stability genes as well as in genes that influence cellular functions like cell cycle, DNA repair, apoptosis, cell adhesion, angiogenesis, and signal transduction that eventually lead to the development and progression of OSCC. Gain of functional mutations or copy number alterations involving proto-oncogenes and/or loss of functional mutations involving TSGs lead to genomic instability tipping the balance toward tumorigenesis. In addition to mutations, epigenetic changes have also been implicated in neoplastic transformation.[20]

Giant cell lesions with cannibalism:

Cellular cannibalism has been reported in a benign tumor called the giant-cell tumor of tendon sheath. It has not been reported in any other benign tumor except giant cell tumor of tendon sheath[21] Cannibalism in malignant tumor is caused due to a shift in the metabolic pathway that encourages a selection of certain cell phenotypes that are able to survive in the caustic environment. These selected malignant cells are highly virulent and cannibalize other malignant cells to survive and progress in adverse condition within microenvironment such as hypoxia, low nutrient supply, and acidity. This pathogenesis is not applicable to benign tumors such as Peripheral Giant Cell Granuloma (PGCG) and Central Giant Cell Granuloma (CGCG). The Giant Cells (GCs) of these pathologies are derived from monocyte-macrophage lineage one such cell being osteoclastic giant cells. Hence, GCs in PGCG and CGCG possess inherent property of engulfment which is responsible for cannibalism of stromal tumor cells. It is believed that increased cannibalistic GCs in PGCG and CGCG represent high metabolic activity in the GCs and could be correlated with aggressive biological behavior of the tumor.[22]

Conclusion

A study by Lugini *et al* showed that melanoma cell lines derived from metastatic lesions exhibited cannibalism, whereas primary tumors did not show this phenomenon. Indeed, cannibalistic activity has been shown to be significantly associated with increased metastatic melanoma cell survival, particularly under starvation conditions. Sarode et al found that the poorly differentiated OSCC reported more number of cannibalistic cells per high power field as compared to moderately differentiated OSCC and concluded that cannibalism is a vital marker of aggressive biological behavior in OSCC. Furthermore, in a study on central giant cell granuloma (CGCG) and peripheral giant cell granulomas, found in aggressive CGCG, mean cannibalistic giant cell frequency was significantly higher than nonaggressive type. Cellular cannibalism has easily identifiable morphological features under light microscopy without the use of any advanced and expensive molecular techniques. Hence, aggressiveness of the neoplasm can be assessed on a routine basis.

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