AN OVERVIEW ON “CELLULAR CANNIBALISM” WITH SPECIAL REFERENCE TO ORAL SQUAMOUS CELL CARCINOMA

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Cellular cannibalism has been defined as a large cell engulfing a slightly smaller one within its cytoplasm. It has been described in various cancers like bladder cancer, breast cancer, lung cancer, gastric cancer, oral squamous cell carcinoma. Cellular cannibalism has been well correlated with anaplasia, tumor aggressiveness, grading and metastatic potential. Present review focuses on significance of cannibalism in relation to cancer with special emphasis on oral squamous cell carcinoma.

Key Words: cannibalism, phagocytosis, cancer, oral squamous cell carcinoma.

The term “cannibalism” is derived from Spanish canibal in connection with alleged cannibalism among Caribs. Also, called as anthropophagy in Greek, i.e., act or practice of humans consuming other humans [1, 2]. Actually, cannibalism is a common ecological interaction, occurring naturally in variety of species. Although there are different types of cannibalism, size structured cannibalism being the commonest form in which large individual feeds on smaller ones. Cannibalism occurs at cellular level in humans also [3]. Cellular cannibalism (CC) is defined as the ability of a cell to engulf another living cell leading eventually to death of internalized cell [4]. Unicellular organisms as well as single cells from multicellular organism are capable of centering their entire efforts for accomplishing their feeding requirements, which is mandatory for survival. Experiments have revealed two phenomena, namely self-cannibalism (macroautophagy) and xeno-cannibalism, i.e., engulfing and digesting cell siblings as well as cells from the immune system. It has been hypothesized that these two processes could be interrelated, xeno-cannibalism being representing exacerbation of self-cannibalism thus offering prolific survival benefit to cells [5].

CELLULAR CANNIBALISM: HOW IT DIFFERS FROM OTHER CELL-IN-CELL PHENOMENON?

Entosis. Entosis is a homogeneous cell-in-cell invasion while cannibalism can be either homogeneous or heterogeneous. In entosis, live epithelial cells or tumor cells detach from extracellular matrix and then invade their neighbor cells. Entosis rely on conjugations or adherens junctions and needs Rho and ROCK activities for internalization, suggesting that entosis is an active process and requires actin polymerization [6].

Emperipolesis. Emperipolesis is a heterogenous cell-in-cell invasion in which engulfed cells are hematoopoietic. The cells are only temporarily internalized and are not destroyed [1, 2].

Efferocytosis. The recognition and elimination of apoptotic cells by tissue macrophages and non-professional phagocytes such as epithelial cells, endothelial cells, fibroblasts and neutrophils known as efferocytosis is critical for development, tissue homeostasis and resolution of inflammation. It is different from other types of cell-in-cell phenomena both cytologically and biologically [7].

Phagocytosis. A brief summary of the differences between CC and phagocytosis is presented in the Table.

Table. Comparison of CC and phagocytosis as two distinct modes of cell-in-cell invasion

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>CC</th>
<th>Phagocytosis</th>
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<tr>
<td>Nature of mecha-</td>
<td>Very calm phenomena</td>
<td>Very expensive and dramatic process</td>
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<td>nism</td>
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<td>Type of cells af-</td>
<td>Feeds on live cells</td>
<td>Feeds on dead cells and toxic materials</td>
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<td>fected</td>
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<td>Mechanism</td>
<td>In this phenomenon, free cell</td>
<td>In this process, macrophage, embrace, surround and engulf</td>
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<td>of action</td>
<td>lay down on the membrane</td>
<td>external body through</td>
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<td>of cannibal cells and then sud-</td>
<td>formation of huge and</td>
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<td>ddenly get into the tumor cells</td>
<td>long pseudopod</td>
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<td></td>
<td>and gradually degenerate and</td>
<td>Associated with scavenging activity triggered by starvation</td>
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<td>dies off</td>
<td>in normal cells</td>
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<td>Type of activity</td>
<td>Associated with feeding and</td>
<td>Usually seen in tumor cells</td>
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<td></td>
<td>is increased in condition of low</td>
<td>Cannibalistic cells are resistant</td>
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<td>nutrient supply. Aimed at sur-</td>
<td>to low pH. Acidic conditions increases CC</td>
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<td>viving in unfavorable condition.</td>
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<tr>
<td>Role of pH</td>
<td></td>
<td>Macrophages usually die at low pH</td>
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<tr>
<td>Role of caveolin-1</td>
<td>Caveolae-mediated endocytosis has a key role</td>
<td>Not involved</td>
</tr>
<tr>
<td>Role of cathepsin-B</td>
<td>Overexpression of cathepsin-B noted</td>
<td>Not involved</td>
</tr>
<tr>
<td>Role of ligand-receptor interaction</td>
<td>No specific ligand-receptor interaction seen</td>
<td>Protein-protein interaction noted</td>
</tr>
</tbody>
</table>

CELLULAR CANNIBALISM AND CANCER

CC has been frequently observed in vivo in several benign and malignant tumors including breast carcinoma [8], giant cell carcinoma of lung [9], endometrial stromal sarcoma [10], malignant melanoma [11], gastric adeno- carcinoma [12], giant-cell tumor of the tendon sheath [4], lung carcinoma, gall bladder carcinoma [13], giant cell granuloma of the oral cavity [14], salivary duct carcinoma [15], oral squamous cell carcinoma (OSCC) [16–19]. These tumor cells cannibalize their siblings as well as cells from the immune system in order to sustain and defend existing unfavorable conditions within the microenvironment such as hypoxia, lack of nutrition and acidity.

Submitted: June 14, 2015.
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Abbreviations used: CC — cellular cannibalism; NTCC — neutrophil-tumor cell cannibalism; OSCC — oral squamous cell carcinoma.
**Cellular cannibalism — morphology and appearance**

CC in cytological or histological preparation is manifested as a cell that is contained within another bigger cell with a crescent shaped nucleus (Fig. 1). This particular appearance is attributed to the fact that ingested cell is contained in a big vacuole that pushes the nucleus of cannibalistic cell to the periphery [19]. Owing to such appearance it was described by Leyden in 1904 as “bird-eye cells” [20].

**Process of cellular cannibalism**

Fig. 2 illustrated the main successive steps of cannibalism as proposed by Brouwer et al. [21].

(A) Cannibalism occurs so that tumor cells can feed on ingested cells thus obviating tumor cell nutritional deficiencies. Experiments have shown that cannibalism is never observed in serum-free cultures but can be reinduced by serum exposure. Also, ultrastructural examination revealed scanty lysosomal content in cannibalistic cell in comparison with free thus proving that death and disintegration of the interiorized cell is due to starvation rather than the action of lysosomal enzymes [21].

(B) CC may function as a way of eliminating malignant cell thus keeping a check on tumor growth [1]. Brouwer et al. demonstrated that serum dependent cannibalism may contribute to the autodestruction of cells and frequent failure to establish human small cell carcinoma of lung cell lines [21].

(C) Few reports suggested that tumor cells have also taste for other non-sibling cells or immune cells like neutrophils, lymphocytes and erythrocytes and may cannibalise them [11, 12, 15, 16, 22, 23]. Such type of conduct signifies that cannibalistic tumor cells cannot discriminate between tumor infiltrating immune cells and sibling neoplastic cells and thus may use cannibalism as a mechanism of tumor immune escape [1].

**Factors regulating cellular cannibalism**

Following factors are known to control phenomenon of cannibalism:

(I) Hunger of the tumor cells/low nutrient supply [1, 4].

(II) Tumor microenvironment, i.e., acidity and hypoxia. Carcinogenesis (malignant tumors) results in acidic microenvironment owing to shift in the metabolic pathway which in turn favors selection of certain cell phenotypes that engulf sibling cells and are able to sustain and survive such adverse environment [4, 24, 25]. This pathogenic mechanism is not relevant to be-
nign tumors such as peripheral giant cell granuloma and central giant cell granuloma. The giant cells of these pathologies are derived from monocyte-macrophage lineage and resemble osteoclasts thus possessing inherent property of engulfment, which is responsible for cannibalism of stromal tumor cells [26].

III Dynamic link between caveolin-1, actin cytoskeleton and ezrin. This network has a key role in formation of cannibalistic vacuole and caveosome and is driving force for cannibalism [4, 27].

IV Overexpression of cathepsin B and acidic milieu of lysosomal like vesicles typify cannibalistic cells [4, 22, 27].

**Cellular cannibalism: assessment parameters**

Cannibalism can be assessed by following parameters [28]:

(I) cellularity of cannibalism — it is semiquantitatively assessed as: (1+) < 5 cells, (2+) 5–20 cells and (3+) > 20 cells in each preparation. Jose et al. graded cellularity of cannibalism as Grade I (< 5 cells), Grade II (6–15 cells) and Grade III (> 16 cells) [18];

(II) diameter of cannibalism — analyzed using an image analysis system;

(III) chromatin pattern — evaluated as heterochromatin pattern or euchromatin pattern;

(IV) background — assessed as necrosis, isomorphic erythrocytes and dysmorphic erythrocytes;

(V) vimentin reactivity.

**Cellular cannibalism as a cancer predictor**

CC is promising marker of anaplastic grade and invasiveness as well as could serve as a valuable tool in assessing tumor behavior [8]. Barresi et al. [29] suggested that neutrophil-tumor cell cannibalism (NTCC) may be one of the mechanisms favoring tumor growth in gastric micropapillary carcinomas, a tumor histotype characterized by aggressive behavior and poor prognosis. Alok et al. [8] assessed cannibalism in 62 cytologically diagnosed cases of breast malignancies and found that CC was more frequent in high grade tumors, thus considering CC as a marker of anaplasia and aggressive tumor behavior. Study by Bansal et al. [13] illustrated that presence of CC in malignant effusions is more often an indicator of higher tumor stage. Also, cannibalism may act as a reliable predictor of tumor progression from primary to the metastatic site.

Aneuploidy is one of the characteristic features of human cancers and polyplody being a precursor to aneuploidy during tumor progression. Polyplody cells can originate from cell fusion, endoreplication, and cytokinesis failure. Recently Krajcovic et al. [30] found that cell cannibalism by entosis also leads to polyplody, as internalized cells disrupt cytokinesis of their engulfing cell hosts. Thus this mechanism can affect cannibalistic cell behavior and could prop up tumor progression by leading to aneuploidy.

Recent studies have demonstrated that horizontal or lateral DNA transfer between eukaryotic cells can occur via uptake of apoptotic bodies and could be attributed for aneuploidy and chromosomal instability responsible for tumor formation and progression [31].

**CELLULAR CANNIBALISM AND ORAL SQUAMOUS CELL CARCINOMA**

CC is one of the typical morphological traits often observed in aggressive malignancies, although it has been demonstrated in certain benign tumors also. It has also been considered as an indicator of aggressiveness, anaplasia and metastatic potential [16, 17]. CC 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.

**Cellular cannibalism as a prognosticator of oral squamous cell carcinoma**

Jose et al. [18] evaluated 20 neck dissection cases of OSCC and found statistically significant correlation between advanced grade of CC and positive lymph node metastasis. So, the authors concluded that CC can be considered as one of the important parameter to assess an aggressive nature of OSCC.

Sarode SC and Sarode GS (2013) screened 30 cases (25 moderately differentiated and 5 poorly differentiated) of OSCC for the presence of cannibalism and found more number of cannibalistic cells in poorly differentiated OSCC compared to moderately differentiated OSCC [17]. No statistical difference between clinical staging of OSCC was found. Also, they have done immunohistochemical analysis with lysozyme and CD68 to validate cannibalism phenomena and demonstrated 10 lysozyme-positive and 5 CD68-positive cases with cell cannibalistic features. Sarode SC and Sarode GS (2014) analysed OSCC for identification of NTCC and found that those OSCC cases which showed extreme NTCC were poorly differentiated and had cervical lymph node metastasis [16]. Thus, NTCC in OSCC could serve as valuable prognostic marker and can foretell biological behavior.

**Complex cannibalism and oral squamous cell carcinoma**

Sarode et al. [19] studied 5 cases of OSCC and observed bizarre morphological appearance cells where one malignant cell was engulfing the other one and this complex was further engulfed by another cell. So, they proposed a newer terminology to the phenomenon as “complex cannibalism”. Maximal number of cannibalistic cells and complex cannibalism was reported in advanced stage and poorly differentiated OSCC. Hence, they concluded that complex cannibalism could be suggestive of highly aggressive biological behavior in OSCC.

**CONCLUSION AND FUTURE PERSPECTIVE**

CC has been proved to be important morphological parameter and has been described in a variety of cancers. It has been well allied with anaplasia, tumor aggressiveness, grading and metastatic potential. Hence it is recommended to screen each cancer specimen for identification of cannibalism to validate its role as a morphological predictor. Literature search fetched up few studies regarding tumor cell cannibalism and OSCC and
therefore warrants call for future elaborative researches to justify role of CC as prognosticator of OSCC. Moreover, future studies should also emphasize on underlying biochemical and molecular aspects of CC.

REFERENCES