

Hunger for Survival in Cancer Cells

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“In the lord’s prayer, the first petition is for daily bread. No one can worship god or even love his neighbors on empty stomach.”
Woodrow Wilson

Food has supreme importance in our day-to-day life. Even in Maslow’s hierarchy of basic needs, food is kept at the bottom of the pyramid. According to physiology and biochemistry of human body, a human being can survive without food for around 40 days and without food and water for only 12 days. Mysteriously, under extreme starving conditions, “human cannibalism” has been reported. Animals, insects and even bacteria have shown evidence of cannibalism.

Cancer cells are characterized by increased mitotic and metabolic activity. Hundreds of signaling pathways are activated for cell proliferation, migration, invasion, and angiogenesis. All these activities need a good supply of nutrition, and hence it is stated that cancer cells consume 15 times more glucose than normal cells. Technically, cancer cells are the only cells in human body, which can have compromised nutritional supply and thus can strategically perform cannibalism of other sibling cells for their survival. This phenomenon is called “cellular cannibalism.”

The first evidence of cannibalism was reported a century ago as a histopathological feature of cell bodies inside the cytoplasm of cancer cells. Further studies have thrown insight into this phenomenon with a demonstration of engulfment of inert particles and dead siblings. Later, cannibalism was described as “smaller tumor cells in the cytoplasm of larger tumor cells with crescent-shaped nuclei.” Recently, cellular cannibalism has received much attention in histology-based studies in oral squamous cell carcinoma.¹⁻³ With more and more studies published in the literature, many morphological guidelines have been proposed. However, the eccentrically placed crescent shaped nucleus and clear halo surrounding internalized cell are the hallmark for identification of cannibalism on histopathological examination.

It is said that pathologies never read books before manifesting themselves and hence exceptions are inevitable in histopathology. Cellular cannibalism also showed exceptions like a small cell engulfing a larger cell, irregular shape of host nucleus (instead of typical crescent shape), pseudopod formation, complex cannibalism, etc. Internalized cell always undergoes lysozyme-mediated degradation, which usually appears as a small eosinophilic area surrounded by a clear halo in the host cell.² However, such clear halo may not always be present. We believe that pathologist should be aware of such exceptions in the histopathological appearances of cellular cannibalism as it helps in predicting the biological behavior of cancer.

Many a times pathologist encounters cancer cells engulfing different types of cells (non-sibling) which is called xeno-cannibalism. Such cells are usually hematopoietic cells, which may include neutrophils, lymphocytes, and red blood cells. In this regard, there is only one study published in the literature on neutrophil tumor cell cannibalism in oral squamous cell carcinoma.⁴ In phenomenon called emperipolesis, the hematopoietic cells actively invade into the host cells/cancer cells. However, it is different from cannibalism, in that the hematopoietic cell (internalized cell) will not undergo degradation but host/cancer cell may show degradation. However, based on the histopathological appearance, it is impossible to differentiate xeno-cannibalism from emperipolesis.

One more cell within cell phenomenon called entosis is purely based on the phenomenon of cell detachment. For survival, detached cells usually undergo internalization into adjacent host cells. In this phenomenon, detached cells are active in invading into the host cells. Similar situation can arise in acatholytic squamous cell carcinoma, which is characterized by cell detachment phenomenon. In

our previous publication, we have reported four cases of acatholytic squamous cell carcinoma showing cell within cell appearance in the detached cells. Technically speaking, this should be categorized under the heading of entosis. But hypothetically, detached cells are usually cutoff from their nutritional supply and hence such cells can potentially show cannibalistic activity for their survival. Hence, the possibility of cell in cell phenomenon as cannibalistic activity in acantholytic squamous cell carcinoma cannot be ruled out. More studies are needed at the molecular level to exactly establish the reason for such abnormal behavior of cancer cells.

The aspect, which baffles us, is the association of cellular cannibalism with malignancy. Every paper published in the literature stated that “cellular cannibalism is exclusively seen in malignancy.” In contrast to this, we have reported cellular cannibalism in benign lesions like central and peripheral giant cell granulomas.⁵ The cannibalistic cells were giant cells which showed engulfment of mononuclear stromal cells. Being associated with monocyte-macrophage lineage, giant cells possess inherited potential for engulfment of phagocytosis/engulfment and thus cannibalism in giant cells may not be associated with hunger. We strongly recommend future research in the aforementioned directions to unveil the behavioral aspects of such cells.

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