

## Cellular Cannibalism in Oral Squamous Cell Carcinoma: An Overview

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### Abstract

Cellular cannibalism" in oral squamous cell carcinoma refers to a phenomenon where cancer cells engulf and consume other cells within the tumor, often considered a marker of aggressive tumor behavior, indicating a high potential for invasion and metastasis; essentially, the cancer cells "eat" each other to survive and proliferate in harsh conditions within the tumor microenvironment. Cannibalism is a completely different entity than phagocytosis, entosis, and emeriopoliosis. It is an important morphologic feature to distinguish benign from malignant lesions. Cannibalism has been described in various cancers such as, bladder cancer, breast cancer, lung cancer, etc, and this is related with the aggressiveness of the malignancy.

**Keywords:** *Cannibalistic, Malignancy, Phagocytosis*

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### Introduction

Cellular cannibalism, defined as the process where one cell engulfs another of the same type, has emerged as a significant hallmark of malignancy, particularly in oral squamous cell carcinoma (OSCC). This phenomenon is not merely an aberration but a complex and adaptive behaviour that may play crucial roles in cancer biology. Understanding cellular cannibalism in OSCC is vital for developing more effective treatment strategies and improving patient outcomes. This review aims to provide an in-depth overview of the biological significance, underlying mechanisms, and clinical implications of cellular cannibalism in OSCC, along with future directions for research in this area.

### Biological Significance of Cellular Cannibalism

Cannibalistic cells, also referred to as cell-in-cell (CIC) structures, are frequently observed in various malignancies, including OSCC (Fig 1).<sup>1</sup> Studies have shown that the presence of these structures correlates with higher tumour grades, increased metastatic potential, and poorer prognosis for patients.<sup>2,3</sup>

The phenomenon of cellular cannibalism is particularly significant in OSCC for several reasons:

#### 1. Survival Advantage

In the context of tumour biology, cellular cannibalism offers a substantial survival advantage to cancer cells. By engulfing and digesting neighbouring cells, particularly in

nutrient-deprived microenvironments, OSCC cells can scavenge essential nutrients and energy sources. This nutrient acquisition is crucial for their growth and proliferation (Fig 2).<sup>4</sup>

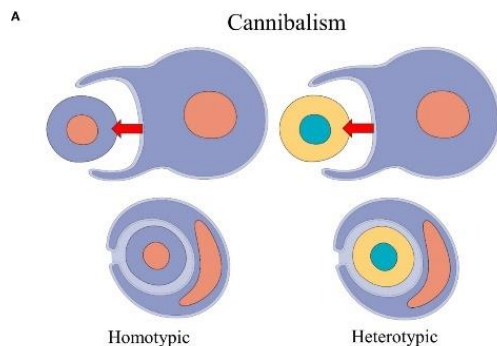


Fig 1: Cellular cannibalism in OSCC.

In solid tumours, where the availability of oxygen and nutrients can be limited due to aberrant blood vessel formation, cannibalistic behaviour allows cancer cells to survive under harsh conditions. This behaviour has been observed in various studies, highlighting that OSCC cells with higher levels of cannibalism exhibit increased resilience against nutrient scarcity.<sup>5-7</sup>

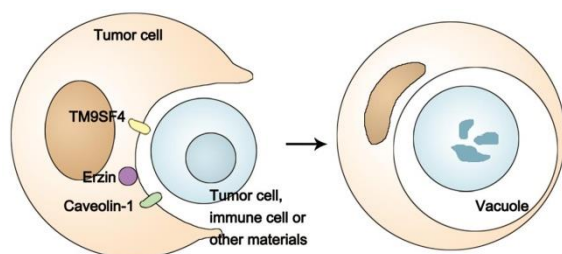


Fig 2: Nutrient acquisition through cellular cannibalism in cancer cells.

## 2. Immune Evasion

Another critical aspect of cellular cannibalism in OSCC is its role in immune evasion. Cancer cells can engulf immune cells, such as lymphocytes, thereby effectively eliminating a key component of the host's immune response. This ability to evade immune surveillance not only promotes tumour growth but also contributes to the overall aggressiveness of the cancer.

Studies have indicated that cannibalistic cancer cells may utilize engulfed immune cells to mask their own antigenic properties, thereby escaping detection by the immune system.<sup>7,8</sup> This capability poses a significant challenge in the treatment of OSCC, as traditional therapies often rely on an intact immune response to be effective.

## 3. Genetic Diversity

Cellular cannibalism can also contribute to genetic diversity within tumours. By incorporating genetic material from engulfed cells, OSCC cells can increase their genetic variability. This variability is advantageous for tumour adaptation, allowing cancer cells to evolve and resist therapeutic interventions.<sup>9</sup>

Moreover, this genetic mixing may lead to the emergence of subclonal populations within the tumour that possess distinct survival advantages, further complicating treatment strategies. Understanding the genetic implications of cannibalism is crucial for future therapeutic approaches targeting these dynamic populations.

Recent studies have specifically linked cellular cannibalism to adverse outcomes in early-stage oral tongue squamous cell carcinoma (OTSCC). This suggests that assessing the degree of cannibalism in tumours may serve as an important prognostic marker.<sup>10,11</sup>

## Mechanisms Underlying Cellular Cannibalism

The mechanisms that drive cellular cannibalism in OSCC are still being actively investigated, but several key pathways have been identified that facilitate this intriguing process:

### 1. Actin Cytoskeleton Remodelling

One of the first steps in cellular cannibalism is the significant remodelling of the actin cytoskeleton. This process is essential for the physical engulfment of other cells. Actin and myosin, two key cytoskeletal proteins, are crucial for facilitating the

morphological changes that allow a cell to extend its membrane and internalize another cell.<sup>8,12</sup>

This dynamic remodelling of the cytoskeleton is not only a physical alteration but also involves signalling pathways that regulate actin dynamics. Disruptions in these pathways can impact the efficiency of cannibalistic behaviour, potentially providing therapeutic opportunities to inhibit this process in OSCC (Fig 3).<sup>13</sup>

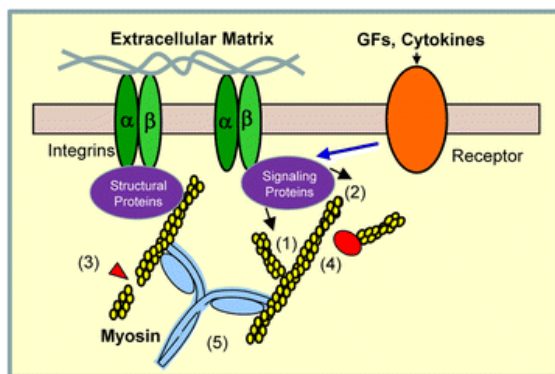


Fig 3: Role of the actin cytoskeleton

## 2. Adhesion Molecules

Altered expression of cell adhesion molecules is another critical factor that facilitates cellular cannibalism. Molecules such as E-cadherin and integrins play pivotal roles in mediating intercellular interactions necessary for engulfment. In OSCC, changes in the expression patterns of these adhesion molecules can promote the binding and internalization of surrounding cells.<sup>12</sup>

The manipulation of these adhesion pathways may serve as a therapeutic target, allowing for the development of strategies aimed at preventing cellular cannibalism and its associated advantages.

## 3. Autophagy Pathways

Cannibalism is closely linked to autophagy, a cellular process involved in degrading and recycling cellular components. Proteins such as LC3 and Beclin-1 are essential mediators in this process. When a cancer

cell engulfs another cell, it can utilize autophagic machinery to break down the internalized material, effectively utilizing it for its own survival.<sup>14</sup>

Understanding the interplay between cannibalism and autophagy could reveal new therapeutic targets that disrupt this process, potentially limiting the growth of OSCC.

## 4. Signalling Pathways

Signalling pathways such as PI3K/AKT and mTOR are critical regulators of cellular survival and metabolism in cancer. These pathways modulate the metabolic adaptation of cancer cells, enabling them to thrive in challenging environments.<sup>7,14</sup>

Research indicates that these pathways may also regulate cannibalistic behaviour, further underscoring their importance in the pathology of OSCC. Targeting these pathways could represent a novel approach to inhibiting cellular cannibalism.

Recent advancements in the field have utilized in vitro 3D spheroid models to provide deeper insights into the formation of CIC structures and their contributions to tumour invasiveness. These models allow researchers to observe the complex dynamics of cannibalism in a more physiological context, enhancing our understanding of the underlying molecular mechanisms.<sup>15</sup>

## Clinical Implications

The presence of cannibalistic cells in OSCC has several important clinical implications that could influence patient management and treatment strategies:

### 1. Prognostic Marker

The frequency of cellular cannibalism in OSCC has been correlated with poor prognosis. Studies have shown that higher levels of cannibalism are associated with increased metastatic potential and reduced survival rates. This association makes cellular cannibalism a potentially valuable

prognostic marker for assessing the aggressiveness of OSCC.<sup>15</sup>

## 2. Therapeutic Target

Targeting the pathways involved in cellular cannibalism presents a promising therapeutic avenue. Inhibiting actin remodelling, autophagy, or adhesion molecule pathways could diminish the survival advantage conferred by cannibalistic behaviour, leading to improved treatment outcomes.

For instance, strategies that block the signalling pathways regulating actin dynamics may prevent the structural changes necessary for engulfment, thus limiting the ability of cancer cells to scavenge nutrients from their neighbours.<sup>12</sup>

## 3. Treatment Resistance

Cannibalistic behaviour in cancer cells significantly contributes to resistance against conventional therapies, including chemotherapy and radiotherapy. This resistance may stem from the nutrient-scavenging abilities of cannibalistic cells, which can enhance their survival during treatment. Furthermore, the ability to evade immune responses complicates the effectiveness of immunotherapies.

Understanding the mechanisms behind treatment resistance associated with cellular cannibalism could lead to the development of novel combination therapies that synergistically target both the cancer cells and the immune system.

## Future Directions

Several promising research directions may help elucidate the full role of cellular cannibalism in OSCC:

### 1. Molecular Profiling

Comprehensive profiling of molecular changes in cannibalistic cells may uncover novel biomarkers and therapeutic targets. Utilizing next-generation sequencing and advanced bioinformatics techniques could facilitate the identification of unique

genetic signatures associated with cellular cannibalism in OSCC.<sup>11,14</sup>

## 2. In Vivo Studies

Employing animal models and advanced in vitro systems, such as 3D tumour spheroids, will be crucial for studying the role of cannibalism in tumour progression and metastasis. These models can provide valuable insights into the dynamics of cellular interactions within the tumour microenvironment and how these interactions influence tumour behaviour.<sup>10,15</sup>

## 3. Therapeutic Interventions

Preclinical testing of inhibitors targeting pathways involved in cellular cannibalism—such as those associated with actin remodelling and autophagy—could pave the way for new treatment strategies aimed at mitigating the impact of this phenomenon on OSCC progression and therapy resistance.<sup>7,10</sup> Clinical trials assessing the efficacy of these targeted therapies are essential to determine their potential benefits in OSCC treatment.

## Conclusion

Cellular cannibalism represents an intriguing and clinically relevant phenomenon in oral squamous cell carcinoma. Its contributions to tumour survival, immune evasion, and genetic diversity underscore its significance in the pathology of OSCC. As research continues to unravel the complexities of cellular cannibalism, there is potential for developing novel prognostic tools and therapeutic strategies. These advances may ultimately improve patient outcomes in OSCC and pave the way for more effective treatments tailored to the unique characteristics of individual tumours.

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