Cell-in-Cell

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Presence of one or more cells (usually viable) inside a cytoplasm of another cell. Inner cell usually resides within a vacuole. Cell-in-cell structure can be developed when one cell engulf second one (in endocytic CICs) or when one cell penetrates into second one's cytoplasm (invasie CICs). There are five known distuinguishable cell-in-cell structure types: cell cannibalism, phagoptosis, enclysis, emperipolesis and entosis

Keywords: cell-in-cell ; entosis ; emperipolesis ; enclysis ; phagoptosis ; cell cannibalism ; adhesion molecules ; cancer

1. Introduction

The advancement of molecular and cell biology in the last century often makes us believe that most, if not all, phenomena which can be observed in light microscopy have already been discovered and described.

However, there exist many unresolved issues in this field, as has been demonstrated by the rediscovery of the process of enclosure of one eukaryotic cell inside another, which is collectively called internalization. This term generally describes the static appearance of one cell enclosed within another cell (cell-in-cell; CIC) and does not focus on its dynamics, i.e., how this state was achieved and what the final fate of those cells will be. The internalization pathway, which may either be heterotypic (between cells of a different type) or homotypic (between cells of the same type), can be induced by an internal (inner, engulfed) or external (outer, engulfing) cell, and can lead to cell death or promote the survival of the involved cells.

Due to the evolving methods of real-time microscopy and the detection of molecules in viable cells, the CIC phenomenon can be now investigated in detail. Since CIC structures are quite rare in tissues, imaging systems should be able to simultaneously observe millions of cells, which is now possible with the novel trans-scale-scope system AMATERAS that consists of a low-power lens and a hundred-megapixel image sensor [1]. Scientific literature is confusing, as it regards the description of different varieties of CICs. In the present review, we try to encompass the entire landscape of the CIC phenomena, discussing the different molecular mechanisms, types of participating cells and outcomes of the CIC process.

From the published reports, it appears that CIC formation may either serve to obtain nutrients [2][3] or escape from harsh environmental conditions [4]. It can also be associated with cancer progression and worse prognosis [5][6]. As we summarized before [7], the CIC process may be modulated by external factors, including: nutrient deprivation [2][8][9], hypoxemia [10], infection, non-adhesive conditions [11][12], and/or presence of distinct chemotherapeutic agents in the extracellular milieu [13][14].

Initially, CIC structures were considered more as a biological curiosity, known only to a few experts in this area. However, there is growing interest in CICs as they could be a novel key factor that regulates cell survival and death. It appears that CICs have prognostic significance in several types of cancer [7]. Moreover, we predict that modulation of this process may be used in the future as a novel therapeutic approach that could influence prognosis, especially in oncological patients.

Are we at the beginning of an era of intense CIC research? Most publications in this field are of high impact (see **Table 1**) [5][6][11][15][16].

Table 1. Analysis of the literature containing selected keywords related to the cell-in-cell phenomenon. Data obtained from Web of Science, refined by publication years: 2007–2021 (as of August 2021). Unambiguous expressions defining a given phenomenon (entosis, enclysis, phagoptosis, emperipolesis) were searched in all fields. Ambiguous expressions (cell-in-cell, cell cannibalism) were searched in the abstract field. In total, there are at least 1000 scientific publications on the subject of cell-in-cell structures, each of which was cited 20 times on average.

Analysis of Cell-in-Cell Literature							
Keyword in Abstract or in Any Field	**Cell-in-Cell (in Abstract)**	**Entosis**	**Cell Cannibalism (in Abstract)**	**Phagoptosis**	**Enclysis**	**Emperipolesis**	**Total**
Number of publications including the selected phrase	**115**	**172**	**147**	**34**	**4**	**540**	**1012**
Total number of citations	**2721**	**6036**	**3790**	**1655**	**16**	**6047**	**20,265**
Average citation per item	**23.66**	**35.09**	**25.78**	**48.68**	**4.00**	**11.20**	**20.02**

However, there appear to be some discrepancies within the published data. There are no recognized CIC standards and criteria. The terms entosis, cannibalism, cannibalistic entosis [13], or heterotypic entosis were used interchangeably [17]. Therefore, we provide a broad overview of the field as a starting point for a larger discussion, and to be able to determine the criteria for the comparison of studies originating from different research groups. We postulate the need for uniform criteria to diagnose CIC phenomena using well-standardized tools, as in the case of apoptosis. To define a cell as apoptotic, we have a number of tools (cytochrome c, caspase assays, PARP, or DNA fragmentation), which can be used reproducibly in different laboratories. However, we lack similar tools to characterize CICs. For example, there is lack of consensus on whether to test LC3, Rho kinase activity, or the dependence of the process on Rho activation as the criteria for CICs [7][11][12].

Therefore, we believe that in-depth research—preferably validated and multicenter—on a large group of tissues and cells is required to be able to look more closely at the CIC phenomenon and identify the factors modulating this process. Correct definition and characterization of CICs is the first necessary step to control this phenomenon, for example, as a therapeutic intervention in cancer.

History of Cell-in-Cell Structures

CIC was originally described in the second half of the 19th century, when Karl J. Eberth reported lymphocytes inside intestinal epithelial cells [18]. Twenty-seven years later, Steinhaus described the first homotypic CIC structures arising between cancer cells [19]. Throughout the 20th century, many similar structures were observed. To describe them, von Leyden introduced the term “cell cannibalism” in 1904 [20]. In 1925, Lewis observed homotypic CIC structures formed by white blood cells [21], while in 1956, Humble described the “active penetration of one cell by another which remains intact”, using the term “emperipolesis” [22].

Recently, two novel CIC structures were discovered, namely entosis [11] and enclysis [23]. Moreover, a new form of cell death by phagocytosis called phagoptosis was proposed [24][25]. Despite significant progress in understanding CICs, there is still a lot to be discovered in the field of cellular interactions.

2. CICs in Physiology and Pathology

Despite the fact that CIC formation still remains poorly understood, preliminary studies suggest the involvement of different processes, collectively described under this umbrella term, in various physiological and pathological mechanisms such as tumor progression, tissue homeostasis, immune response modulation, inflammation, neurodegeneration, platelet membrane circulation, Rosai–Dorfman disease, and many others [26][27][28][29][30][31].

The relationship between CICs and cancer is especially interesting due to possible diagnostic and therapeutic implications. Three types of CICs are potentially involved in cancer progression. Cell cannibalism and entosis support the survival of cancer cells in unfavorable conditions by supplying nutrients to the outer cell [9][32]. Moreover, cell cannibalism and emperitosis are possible ways of overcoming an immune response against them. Cannibalistic cells can engulf and destroy lymphocytes to escape the immune response [32]. Emperitosis is another way of destroying an immune cell before it can attack a cancer cell. The cancer cell rapidly creates a large vacuole around the NK cell, which obstructs the penetration of granzyme B into the cytoplasm and forces the NK cell to re-endocytose granzyme B, leading to its death *via* an apoptotic pathway [33].

Thus, entosis, emperipolesis, and phagoptosis can have cancer-suppressive outcomes. Entosis is a mechanism which can eliminate aneuploid cells from the cellular population, but only when the TP53 gene is not mutated [34]. In emperipolesis, a NK cell enters a cancerous cell to induce its cytolysis from within [35]. Stimulating phagoptosis by modulating the expression of “eat me” and “do not eat me” signals on cancer cells is a promising idea for cancer

immunotherapy. Numerous antibodies are able to induce this process by opsonization [36]. Moreover, combined therapies, including the usage of the CD47 antagonist CV1 with lorvotuzumab (anti-CD56 antibody) can significantly enhance the phagoptosis of cancer cells in small-cell lung cancer [37]. Taking all these data into consideration, entosis and emperipolesis appear to be tumor-suppressive mechanisms in physiological situations. However, cancerous cells are gaining the ability to survive these processes and use them to their own benefit. The CIC phenomena, originally acting to suppress tumor progression, appear to facilitate the survival of cancer cells in unfavorable conditions.

The fifth described type of CIC structure, enclysis, can also be a target of cancer therapy, specifically immunotherapy of hepatocellular carcinoma (HCC). Recent studies have shown that an elevated level of regulatory T cells in cancer tissues is associated with poor HCC cell differentiation and advanced stages of hepatic fibrosis [38]. HCC has also been reported to have a three-fold higher number of regulatory T cells in comparison to healthy tissue [39]. Enclysis is a process which leads to the depletion of Treg cells. Enhancement of this process could alleviate local immunosuppression of the HCC's microenvironment and restore tumor immunogenicity [40]. Taking all these data into consideration, all five types of CICs are potential therapeutic targets in cancers.

CICs are involved in immune response modulation. Suicidal emperipolesis and enclysis are two CIC-forming mechanisms, which enable the liver to control the population of T lymphocytes. The outcomes of these processes are contrary to each other. During suicidal emperipolesis, when an autoreactive naïve CD8+ T lymphocyte recognizes an autoantigen on a hepatocyte, it is engulfed and killed. During enclysis, regulatory T (Treg) lymphocytes are usually killed in the lysosomal pathway while non-Treg lymphocytes survive engulfment [41]. The possible outcome of this process is the enhancement of the immune response. Therefore, hepatocytes have both the ability to induce immune tolerance by eliminating autoreactive T lymphocytes in suicidal emperipolesis and to remove tolerance by directly eliminating Treg cells. These appear to be complementary mechanisms of the immunomodulatory functions of the liver. Nevertheless, proving this hypothesis still requires further studies.

CICs have also been associated with inflammation. It has been reported that the presence of emperipolesis in autoimmune hepatitis correlates with a stronger inflammatory response [29]. Another CIC type associated with inflammation is phagoptosis. Although phagoptosis cannot modulate the immune response, it can enlarge inflammation-mediated tissue destruction such as neuronal loss. β-amyloid in a low concentration does not directly kill neurons, but induces phosphatidylserine (PS) exposure in neurons. The presence of this phospholipid on the outer membrane is an "eat me" signal for microglia. Blocking phagoptosis in such a situation prevents neuronal loss [28]. This confirms the involvement of phagoptosis in neurodegenerative disorders such as Alzheimer's disease.

Overall, it appears that a better understanding of CICs can be helpful in elucidating the etiopathology of many clinical abnormalities (summarized in **Table 4**). Standards, unification, and distinction between CICs can accelerate progress in research since CICs might prove to be useful therapeutical targets. Depending on the type of CIC and circumstances, either enhancing or inhibiting the formation of these structures can have a positive effect on various clinical features.

Table 4. Comparison between different types of CIC structures.

	Cell-in-Cell Structures						
Structure	**Cell Cannibalism**	**Phagoptosis**	**Enclysis**	**Emperipolesis**			**Entosis**
				In General	**Suicidal**	**Emperitosis**	
First description	**1904**	**2012 (name proposed)**	**2019**	**1956**	**2011**	**2013**	**2007**
Mechanism	**Endocytic (phagocytosis-like)**	**Endocytic (phagocytosis-like)**	**Endocytic (pinocytosis-like)**	**Invasive**	**Invasive**	**Invasive**	**Invasive**
Type	**Homotypic or heterotypic**	**Heterotypic**	**Heterotypic**	**Heterotypic**	**Heterotypic**	**Heterotypic**	**Homotypic**
Outer cell	**Cancerous cell, e.g., melanoma**	**Macrophage, microglia**	**Hepatocyte**	**Cancerous cell or megakaryocyte**	**Hepatocyte**	**Cancerous cell**	**Cancerous cell**
Inner cell	**Cancerous cell, leukocyte, mesenchymal stem cell**	**Various, e.g., leukocyte or neuron**	**CD4+ T lymphocyte**	**Leukocyte or erythrocyte**	**CD8+ T lymphocyte**	**NK cell**	**Cancerous cell**

	Cell-in-Cell Structures						
Structure	**Cell Cannibalism**	**Phagoptosis**	**Enclysis**	**Emperipolesis**			**Entosis**
				In General	**Suicidal**	**Emperitosis**	
Fate of the engulfed cell	**Lysosome-mediated cell death**	**Lysosome-mediated cell death**	**Lysosome-mediated cell death (usually Tregs) or escape (usually non-Tregs)**	**Cell death, mitosis, or escape**	**Cell death**	**Apoptotic cell death**	**Cell death, mitosis, or escape**
Triggering factors	**Starvation, acidic environment**	**Presence of "eat me" or lack of "do not eat me" signals (PS, lack of CD47) on an inner cell's surface**	**N/D ***	**N/D**	**N/D**	**N/D**	**Matrix detachment, starvation, mitosis**
Involved molecules	**Ezrin, caveolin-1, TM9SF4**	**PS, antibody, and CD47 receptors**	**ICAM-1, β-catenin**	**(Refer to suicidal emperipolesis and emperitosis)**	**Ezrin, F-actin, CD44**	**Ezrin, E-cadherin, ICAM-2**	**E-cadherin, ezrin, Rho-ROCK-actin/myosin pathway**
Possible biological functions	**Enhancing survival of tumor cells by acquiring nutrients, immune escape, or entering senescence**	**Removal of aging erythrocytes and cancerous cells**	**Modulation of lymphocyte subpopulations (strengthening of the immune response)**	**(Refer to suicidal emperipolesis and emperitosis); destruction of cancerous cells, viral transmission, platelet membrane circulation**	**Autoreactive T lymphocyte deletion**	**Immune escape**	**Removal of aneuploid cells or enhancing cancer survival**
Clinical occurrence	**Metastatic melanoma**	**Cell turnover, Alzheimer's disease**	**The process was reported in healthy individuals**	**Rosai–Dorfman disease**	**Autoimmune hepatitis**	**N/D**	**Nasopharyngeal, breast, lung, pancreatic cancer**

* N/D—not defined.

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