The term “cell-in-cell” refers to a phenomenon in which one living cell enters into another living cell to form a so-called “cell-in-cell structure.” Cell-in-cell has first been observed more than 100 y ago, yet their biological significance has been near-to-completely disregarded since.1 Recently, cell-in-cell has attracted interest as it can be found across a wide range of species (encompassing lower eukaryotes and mammals) and attributes a biological significance in specific pathophysiological conditions.

In vitro cell-in-cell, be they homotypic, heterotypic or xenotypic, has been documented in a wide panel of cell lines.2 As compared with neoplastic cells obtained from solid tumors, hematopoietic tumor cells exhibit an increased propensity of being internalized. The frequency of heterotypic cell-in-cell structures involving one malignant cell and one immune effector cell is higher than that of homotypic ones. Moreover, not all malignant cells undergo homotypic cell-in-cell formation whereas most of them participate in heterotypic cell-in-cell structure with immune effectors.

The fate of cells participating in cell-in-cell is also highly variable (Fig. 1). In some instances, upon internalization effector cells can divide within target cells or penetrate them, in both cases being released alive afterwards. Most often, however, internalized effector cells succumb to cell-in-cell death via 2 partially similar processes: entosis3 or cell-in-cell apoptosis.4,5 Unlike cannibalism, during which metastatic cancer cells undergoing starvation actively “eat” other cells (be them dead or alive, and irrespective of their types) and degrade them in caveosomes,6 entosis proceeds through the lysosomal degradation of internalized cells trapped in the vacuole of host cells (entotic vacuole). In this setting, internalization favors the accumulation of autophagosomes and autolysosomes within host cells and their fusion with the entotic vacuole, in turn stimulating the internalized cell to undergo a unique, autophagosome-independent lysosomal death mode.7 We have recently demonstrated the existence of another cell-in-cell death pathway, i.e., caspase-dependent cell-in-cell apoptosis. This cell-in-cell death modality only concerns in cytotoxic immune effector cells, which upon internalization become prone to undergo apoptosis as triggered by autologous granzyme B.8 Both entosis and cell-in-cell apoptosis are initiated by the formation of an entotic vacuole within the host cell. However, only cell-in-cell apoptosis manifests with a rapid bubbling of the entotic vacuole followed by the re-uptake of autologous granzyme B by the internalized immune killer cells (Cell Death and Disease, forthcoming).

We termed this cell-in-cell death process as emperitosis, from emperipolesis and apoptosis. How cells in the entotic vacuole are recognized by lysosomes in the course of entosis or release granzyme B during emperitosis is still unknown, as are the signals whereby internalized cells undergo different cell-in-cell death processes.

The biological outcome of cell-in-cell has puzzled researchers for a long time, but mainly in relationship to carcinogenesis. Recently the invasion of tissue cells by lymphocytes has been shown to occur at a relatively high frequency also at inflammatory sites.2 Of note, not only the presence of inflammation, but also its type, stage, and severity appear to influence the formation of cell-in-cell structures (unpublished data). In particular, the type of internalized cells varies within different stages of inflammation. Thus, one may wonder why cell-in-cell happens in the first place and what its biological outcomes are. This consideration prompted us to refocus our attention on the fate of host, as opposed to internalized, cells, and how cell-in-cell may modulate the tumor microenvironment. We and others have demonstrated that the entry of internalized living cells into the nucleus of host cells results in the failure of cytokinesis, thus favoring chromosomal instability (CIN) and aneuploidy.2,9 This process appears...
to be independent of the host cell type, as immune cells invade normal cells and transformed cells with a similar efficacy. Upon internalization, immune cells penetrate into the nucleus of host cells, often promoting to multinucleation. Considering CIN as a key feature of inflammation and malignancy as well as the elevated frequency of cell-in-cell structures found at inflammatory sites, it is tempting to speculate that (especially heterotypic) cell-in-cell might constitute a “fast track” for the transformation of normal cells, hence sustaining both oncogenesis and tumor progression.

The existence of cell-in-cell structure within inflamed tissues presumably influences many processes other than tumorigenesis. Cell-in-cell might indeed constitute a unique means to alter the properties of target cells, thus participating in the holistic regulation of the tissue microenvironment during inflammation. The elimination of autoreactive T cells by hepatocytes through cell-in-cell strongly supports the regulatory role of this process in the maintenance of tissue homeostasis. We have also observed the internalization of granulocytes by apoptotic hepatocytes in specimens from hepatitis-infected livers. This might facilitate the elimination of apoptotic hepatocytes and hence accelerate the restoration of homeostasis (S. Hexige, Fudan University, Shanghai, China, personal communication). In addition, the internalization of tumor-infiltrating lymphocytes by malignant cells might hamper antitumor immune responses, thus favoring the evasion of anticancer immunosurveillance. Cell-in-cell appears therefore as an important mechanism to maintain tissue homeostasis and respond to pathogenic stimuli. How cell-in-cell affects the tissue microenvironment and their clinical relevance in the course of tumor progression warrant further investigation.

Cell-in-cell, an old enigma often ignored or questioned by clinicians, has not yet been completely understood. In view of the unexpected complexity of cell-in-cell, we have proposed 2 models that may help the elucidation of the biological significance of this phenomenon: a selection and a stress model. The efforts of additional scientists and clinicians will provide further insights into the impact of cell-in-cell on physiological and pathological processes.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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