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Highlights

Can cannibalizing cancer cells challenge classic cell death classification?

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ABSTRACT

In this issue of the *Biomedical Journal*, we learn about a novel are still largely mysterious mechanism of cell death that is challenging classification systems of cell death pathways and could have important implications for future cancer therapy. We also learn of a promising biomarker to stratify patients into risk groups after stroke. Finally, this issue also includes two studies investigating factors that influence outcome after heart surgery.

Spotlight on reviews

Can cannibalizing cancer cells challenge classic cell death classification?

Within all living multi-cellular organisms, cells are constantly renewed and replenished. The concept of cell death programs like apoptosis as a means to eliminate damaged or undesired cells is a familiar one, but imagine a process in which perfectly viable cells crawl into neighboring cells to die. In this issue of the *Biomedical Journal*, Martins et al. [1] discuss this particular form of cellular cannibalism called entosis, the details and significance of which, are still very much being worked out.

Classically three types of cells death are characterized based on morphological features of these processes: apoptosis (Type I cell death), autophagy (Type II cell death) and necrosis (Type III) cell death. All of these processes are cell autonomous, meaning that they can be triggered independently of other cells. However, this classification system fails to capture the full complexity of cellular death pathways, and in particular various types of non-autonomous pathways that are initiated by neighboring cells. One of such pathways is entosis, in which living cells are absorbed by other living cells.

Entosis was first discovered 10 years ago in cancer cells [2], although researchers had been staring at it through the microscope for well over a century. As early as 1864, Eberth noted "cell-in-cell" structures of epithelial cells containing lymphocytes, which were followed by reports of whole tumor cells inside the vacuole of other tumor cells, giving the appearance of a "bird's eye" (reviewed in Ref. [3]). This engulfment process appeared distinct from phagocytosis because the engulfed cells were alive. Once internalized, engulfed cells are typically eliminated through lysosomal degradation; however, the process itself is not automatic death sentence because sometimes engulfed cells are released from their host and can even divide within the host cell [4].

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We know that entosis is genetically controlled form of cell death because it is repressed by the chromatin factor Nuclear Protein 1 [5]. However, no specific biochemical markers of entosis have been identified yet which makes it difficult to follow and study. Growing evidence suggests that adherent junctions formed of E-cadherins and β-catenins are important for the induction of cell invasion [2], and the engulfment process itself is regulated by the actin-binding protein Erzin [6]. The death mechanisms that ensue are thought to be context-dependent, involving apoptotic pathways in some cases [6] but not in others [2], but eventually culminate in lysosome-mediated destruction of most target cells.

So what could be the physiological significance of this cellular cannibalism? Cell-in-cell structures indicative of entosis have been commonly reported in the context of malignancy for many years. Although it is unlikely to be the only context in which entosis occurs, it is by far the best studied. Depending on the context and type of internalized cell, entosis can be either tumor-suppressive or tumorigenic. Reports showing that entosis ends with the death of engulfed cancer cells support a tumor suppressive role for the process [2,6]. However, melanoma cells are able to cannibalize immune cells and to feed on them, thus ensuring their survival upon starvation and probably leading to immune escape [7]. Entosis may also generate cancer-driving mutations by causing aneuploidy [8], and has even been proposed contribute to competition between cells in tumors leading to the emergence of highly aggressive "winner" clonal populations of cells [9].

Regardless of its mechanisms or role, Martins and colleagues argue that entosis and other atypical cell death processes necessitate a rethinking of our classification system for cell death pathways [Fig. 1]. Proper recognition of its status as a cell death pathway would stimulate further studies on its biological underpinnings and relevance and perhaps even lead to ways to control it, thus unlocking new potential avenues for cancer therapy.

Spotlight on original articles

Neutrophil to lymphocyte ratio predicts outcome in acute ischemic stroke

Ensuring that patients receive the right treatment and follow-up after acute ischemic stroke (IS) remains a major challenge. In this issue of the *Biomedical Journal*, Fang et al. [10] report a biomarker that could help to improve the management one of the most common causes of death and disability worldwide [11].

For most patients with acute ischemic stroke (IS), supportive care and rehabilitation remain the mainstay of treatment. In this setting, a major challenge in ensuring optimal care is the ability to stratify patients into high and low risk groups. The only widely used prognostic markers in clinical practice are age, infarct volume, and National Institutes of Health Stroke Scale (NIHSS) score. Although several other prognostic biomarkers have been proposed, many of these, including microRNA [12] or pro-inflammatory cytokines [13] are expensive and difficult to measure accurately in a clinical setting.

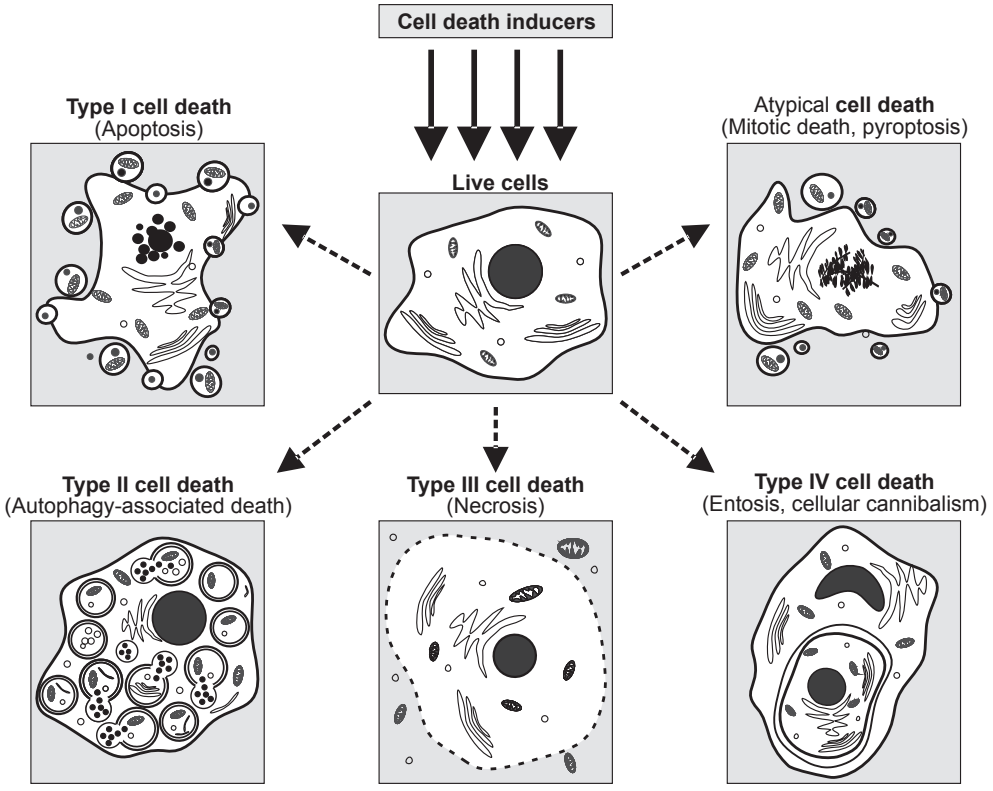

Fig. 1 A potential new classification system for the various types of cell death pathways. Figure kindly provided by Martins et al. [1].