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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.

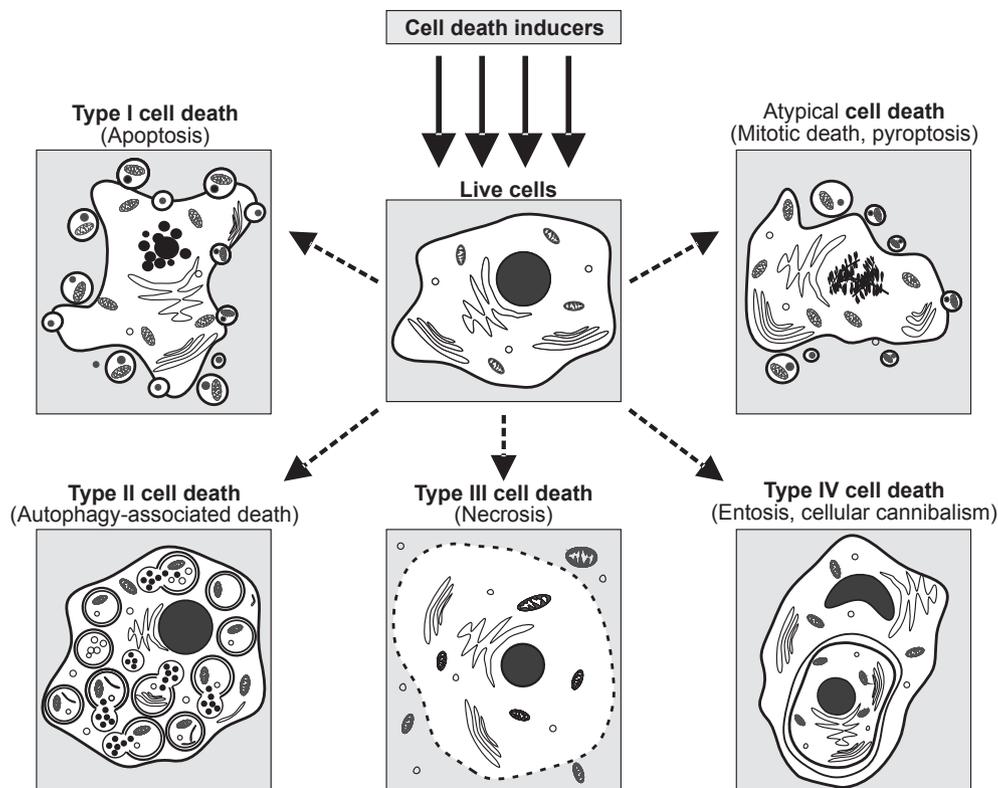


Fig. 1 A potential new classification system for the various types of cell death pathways. Figure kindly provided by Martins et al. [1].

Neutrophils are phagocytic, pro-inflammatory cells that are one of first responders to the site of infection. Their role in inflammation is so important that the ratio of neutrophils to lymphocytes (NLR) is considered a marker of systemic inflammation [14] and is associated with outcome in cardiovascular disease [15,16] and several types of cancer [17,18]. Several small studies suggest that NLR is a valuable prognostic marker in IS patients [19–21]; now Fang et al. [10] attempt to validate these findings in the largest prospective study of its kind.

In this retrospective observational study, Fang et al. examined the medical records of 1731 patients with IS treated at a Taiwanese hospital over a two-year period. Of these patients, 1055 were categorized as having mild stroke, 519 as having moderate stroke and 157 as having severe stroke according to their NIHSS. NLR was positively correlated with severity of stroke, such that those classified as having severe stroke had significantly higher NLR than those classified as having moderate or mild stroke. Among the 25 variables tested, age, previous stroke, congestive heart failure and NLR were significantly predictive of in-hospital mortality according to univariate analysis across all groups. Stepwise logistic regression analysis revealed that NLR was independently associated with in-hospital mortality. The best discriminatory cut-off value was 3.2, with patients with a NLR ≥ 3.2 having a 2.55 fold higher risk of in-hospital mortality than those with a NLR < 3.2 .

These findings validate previous reports that NLR predicts mortality in patients with acute IS and that it should be considered a biomarker for risk stratification in combination with existing prognostic markers like age. Moreover, this simple and inexpensive measure of inflammation may have prognostic value and improve patient management in a wide variety of diseases.

Also in this issue

Review article

Detecting and treating Kawasaki disease

Kawasaki disease is a rare childhood disease in which blood vessels become inflamed, leading to coronary artery lesions if left untreated. In this review, Kuo [22] discusses the symptoms and treatment of Kawasaki disease and in particular how to prevent any associated coronary complications.

Original articles

Metabolic syndrome and hypothyroidism: chicken vs. the egg

Thyroid hormones upregulate metabolism and energy expenditure. Thus, many patients with metabolic syndrome or obesity have hypothyroidism and vice versa although it is not clear which causes which. To resolve this issue, Gutch et al. [23] reason that more studies are needed to examine how thyroid profile is correlated with metabolic hormones and metabolites. Their analysis of 100 patients with metabolic syndrome from Northern India reveals interesting correlations between thyroid hormones and serum lipid profile,

although more large-scale studies are needed to shed light on this chicken-and-egg situation.

Changes after orthopedic surgery in children with cerebral palsy

Orthopedic surgery is a common treatment to prevent or slow the debilitating deterioration in motor function that occurs in children with cerebral palsy (CP). These surgeries improve gait function and reduce chronic morbidity, but their immediate effect on gross motor function is variable and likely to depend on several factors [24,25]. In their analysis of 25 children with CP undergoing multi-level soft tissue release for knee flexion gait, Chang et al. [26] study the profile of changes to gross motor function measure (GMFM) during the recovery period and report that young age predicts high GMFM scores at six months postoperatively. These findings have important implications for rehabilitation planning.

No link between obesity and outcome after heart surgery

Obesity is a well-recognized risk factor for cardiovascular disease. Yet, some studies report that obese patients show a better outcome than non-obese patients after certain types of heart surgery [27,28]. To resolve this “obesity paradox” more large-scale studies are needed to investigate how obesity impacts outcome after heart surgery, particularly in Asian populations, which have thus far been under-represented among such studies. Wu et al. [29] report here that body mass index has no influence on outcome at 30 days in 925 Taiwanese patients with ST-segment elevation myocardial infarction (STEMI) undergoing percutaneous coronary intervention (PCI).

Two heart surgeries are no worse than one

Two principal options exist for revascularization in coronary artery disease: percutaneous coronary intervention (PCI), which involves the use of stents to restore blood flow, and the arguably more drastic, coronary artery bypass surgery (CABG), which involves the use of grafted blood vessels to bypass the blockage. Many patients who have undergone PCI require CABG within a few years [30]; yet, the impact of prior PCI on CABG remains a subject of much debate. Cheng et al.'s retrospective study of 439 patients undergoing CABG [31] supports the idea that prior coronary stenting does not affect short-term mortality in patients undergoing subsequent CABG.

Conflicts of interest

The author declares that there are no conflicts of interest.

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