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Title: In the hunger games, the winner takes everything

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Keywords

Cancer metabolism, starvation, glucose, AMPK, cell death, entosis

Abstract

Entosis is an atypical form of cell death that occurs when a cell engulfs and kills another cell. A recent article by Overholtzer and colleagues indicates that glucose deprivation promotes entosis. AMPK activation in the loser cells triggers their engulfment and elimination by winner cells, which endure starvation.

Text

Cells in our bodies are constantly dying and being replaced by new cells. The best understood form of regulated cell death is apoptosis. However, other forms of cell death are pathologically and physiologically relevant in certain contexts. In some cases, cell death is actively engaged from within the cell, which senses that it is damaged or aged. These subroutines of cell death include the mitochondrial apoptotic pathway and can be called “suicide”. In other cases, cells die when they are attacked by the immune system that senses that they are infected, and are, thus, usually, “murder”. This includes granzyme- and death receptor-mediated apoptosis, and perforin-mediated necrosis. But other intriguing and understudied cell death routines involve the killing of living cells that are selected and phagocytosed by professional phagocytes (phagoptosis, [1]) or by a neighbouring epithelial cell (entosis). These forms of cell death could be labeled as “cannibalism”.

Entosis is a particularly intriguing process by which an –apparently– happily living cell is eaten and killed by an epithelial cell [2]. Entotic structures are detected in human carcinomas, and this observation suggested that entosis could represent a form of competition between cancer cells. This competition involves a winner and a loser cell, and the winner status has been shown to be conferred by oncogenes such as *KRas* [3]. The winner versus loser status is dictated by mechanical deformability, with the loser cell being stiffer and becoming entrapped by the softer cell that engulfs it.

In a recent article, Hamann, Overholtzer and colleagues examined whether the frequency of entotic events in culture could be enhanced by starvation [4]. The group had previously shown that during entosis, recovery of amino acids from entotic corpses contributes to nutrient balance [5]. However, amino acid deprivation did not promote entosis. In contrast, the authors now show that glucose deprivation greatly increased the number of entotic events. Moreover, the time between engulfment and death of the internalized cells was reduced under glucose deprivation.

Glucose deprivation has been shown to induce cell death in several manners, and in many cases simultaneously. Indeed, in the culture conditions employed by Hamann *el al.* [4], some MCF-7 cells died by apoptosis or necrosis along with entosis. However, inhibition of entosis by deleting *E-cadherin*, which had been shown to mediate this process, reduced the total number of dead cells. Deletion of *E-cadherin* or inhibition of the kinase ROCK also increased the percent of necrotic versus apoptotic cells, which suggests interplay between necrosis and entosis. As shown before for spontaneous entosis, LC3, which is involved in autophagy and in phagocytosis of corpses, decorated entotic vesicles. Another similarity with autophagy was that silencing ATG5, a protein involved in autophagy vesicle formation, reduced the number of engulfed cells that could not escape and underwent cell death. Although the effects of silencing ATG5 on the percent of cell death in the whole population were not addressed, this reinforces the notion that macroautophagy does not promote survival of glucose-deprived cells [6]. Interestingly, however, entosis did support proliferation of the winner cells. Moreover, entosis promoted multinucleation and aneuploidy in the population (Fig. 1), suggesting that starvation can promote aneuploidy by inducing entosis, and thus contribute to tumor promotion.

But perhaps the most intriguing finding is what determines whether a cell eats or gets eaten. The authors investigated AMPK, the ATP/AMP sensor, and found that the cells that activate it are the ones that turn “stiffer” and get eaten as a consequence [4]. In fact, activation of AMPK was sufficient to enhance the frequency of entosis in the presence of glucose. The question remains whether, under glucose deprivation, the cells that activated AMPK were more stressed --perhaps because of the cell cycle stage that they were in-- or whether both populations, winner and losers, underwent the same levels of energetic stress but stochastically activated AMPK differentially. Even clonal cell populations in culture are heterogeneous, and in this case, detecting energy failure was lethal.

Several questions arise regarding the evolution and consequences of entosis in this context. Why does AMPK activation promote entosis: is this somehow linked to phagocytosis? It should be mentioned that AMPK is an evolutionarily conserved signal of infection: numerous publications link AMPK activation to viral infection, and on the other hand, AMPK is activated via TAK1 downstream of immune cytokines [7]. This suggests that the detection of a loss of ATP could be evolutionarily linked to detection of infection, and to immune function, and perhaps it is a signal that promotes phagocytosis by neighboring cells. Follow up questions in the context of entosis include: does AMPK promote exposure and/or secretion of "eat me" signals? Which classical “eat me” signals are associated with entosis? On the other hand, how is AMPK linked to the mechanical changes involved in entosis? The recent finding that AMPK participates in mechanotransduction should help clarify mechanistic details [8].

Metabolic stress, and particularly, glucose starvation have been shown to promote multiple different forms of cell death, ranging from necrosis to atypical necroptosis or mitochondrial apoptosis, and more recently, death receptor-mediated apoptosis [9, 10]. We should now add cannibalism to the list of typical and atypical cell death subroutines engaged by lack of nutrients.

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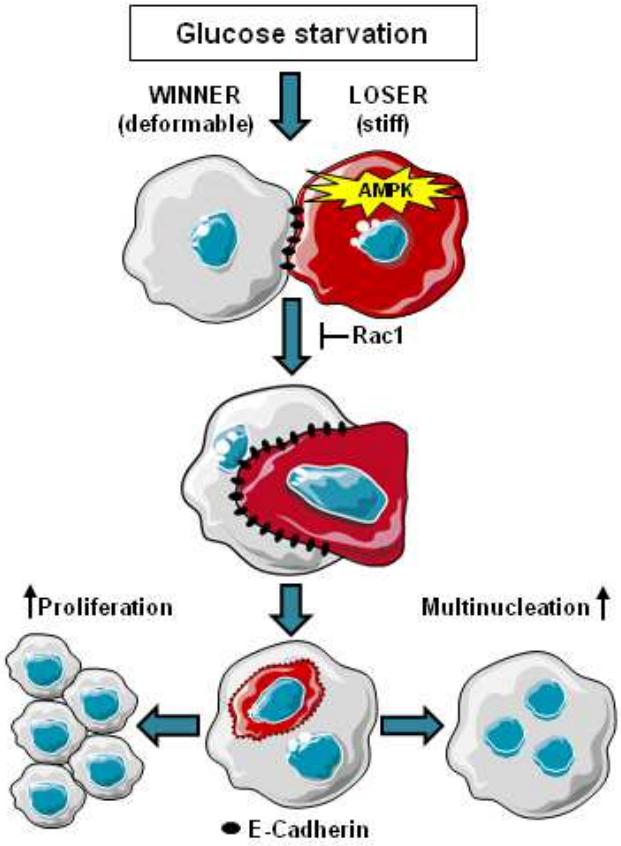

Figure 1: Glucose starvation promotes entosis mediated by AMPK induction

Metabolic stress induced by glucose starvation results in induction of entosis. This is mediated by activation of the energy sensor AMPK in the loser cells accompanied by a stiffer cell phenotype. In contrast, winner cells show a more deformable phenotype after glucose starvation. Entosis is facilitated by ROCK signaling and can be blocked by Rac1 induction. Subsequent engulfement of loser cells supports winner cells with nutrients promoting multinucleation, proliferation and survival.