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Unconventional Ways to Live and Die: Cell Death and Survival in Development, Homeostasis, and Disease

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Abstract

Balancing cell death and survival is essential for normal development and homeostasis and for preventing diseases, especially cancer. Conventional cell death pathways include apoptosis, a form of programmed cell death controlled by a well-defined biochemical pathway, and necrosis, the lysis of acutely injured cells. New types of regulated cell death include necroptosis, pyroptosis, ferroptosis, phagoptosis, and entosis. Autophagy can promote survival or can cause death. Newly described processes of anastasis and resuscitation show that, remarkably, cells can recover from the brink of apoptosis or necroptosis. Important new work shows that epithelia achieve homeostasis by extruding excess cells, which then die by anoikis due to loss of survival signals. This mechanically regulated process both maintains barrier function as cells die and matches rates of proliferation and death. In this review, we describe these unconventional ways in which cells have evolved to die or survive, as well as the contributions that these processes make to homeostasis and cancer.

Keywords

apoptosis; extrusion; anastasis; autophagy; necrosis; cell death

INTRODUCTION

The regulation of cell death and survival is fundamental for eukaryotic development and tissue homeostasis. It is as important for autoreactive T cells, supernumerary cells, and damaged cells to die as it is for stem cells, cardiomyocytes, and neurons to last our whole lives. Eukaryotic cells can die by accident, suicide, or murder. Accidental cell death, usually as a result of severe stress, is not under the control of specific genes or gene products, whereas regulated cell death, whether suicide or murder, is mediated genetically and tightly controlled (Galluzzi et al. 2015). Necrosis is a common form of accidental cell death

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characterized by cellular swelling and loss of membrane integrity (Vanlangenakker et al. 2012). Apoptosis, the most extensively studied form of regulated cell suicide, is characterized as a series of stereotyped morphological changes in response to the activation of proteolytic enzymes termed caspases (Kerr et al. 1972, Vaux 2002). Autophagic cell death (ACD) occurs when cytosolic autophagic vacuoles consume the cell (Liu & Levine 2015).

Since identification of these canonical cell death mechanisms, new studies have revealed strikingly diverse ways by which death pathways can be triggered, regulated, and even reversed. Death by pyroptosis, necroptosis, and ferroptosis turns out to be regulated rather than accidental. Additionally, death by live cell engulfment occurs in the processes of phagoptosis and entosis. Surprisingly, cells can recover from the brink of several forms of death, including apoptosis, necroptosis, and entosis, in some cases after passing through biochemical steps previously considered points of no return, such as activation of executioner caspases. This review covers our current understanding of conventional and unconventional cell death and survival programs.

CONVENTIONAL FORMS OF CELL DEATH

Apoptosis

Apoptosis, the best-characterized form of programmed cell death, is essential for normal animal development, tissue homeostasis, and disease and has been reviewed extensively elsewhere (Elmore 2007, Fuchs & Steller 2011, Taylor et al. 2008). Morphological hallmarks of apoptosis include cell shrinkage, membrane blebbing, nuclear condensation, and DNA fragmentation. Classical biochemical markers of apoptosis include mitochondrial outer membrane permeabilization (MOMP); activation of a group of proteases termed caspases; and the externalization of phosphatidylserine, which attracts phagocytes that engulf apoptotic cells without inducing an inflammatory response (Martin & Green 1995, Taylor et al. 2008). Apoptosis can result from active prodeath signals or from loss of survival signals. Anoikis is a specific type of apoptosis resulting solely from loss of survival signals derived from attachment to extracellular matrix (ECM) and/or neighboring cells (Frisch & Francis 1994). Anoikis is a common form of cellular murder whereby neighboring cells squeeze a cell out by the process of extrusion (Eisenhoffer et al. 2012, Rosenblatt et al. 2001).

Apoptosis is triggered when prodeath signals outweigh prosurvival signals. Once the balance is tipped, cells activate upstream initiator caspase-8 or −9; these caspases cleave and activate executioner caspases-3 and −7 (Salvesen & Ashkenazi 2011). Executioner caspases cleave hundreds of cellular targets, resulting in biochemical and morphological hallmarks and ultimately death (Coleman et al. 2001, Lakhani 2006, Lüthi & Martin 2007, Martin et al. 1995). If caspase activity is blocked, cells can still sometimes die by caspase-independent cell death (Tait & Green 2008). Although activation of executioner caspases has been considered a point of no return in the apoptotic pathway (Green & Kroemer 1998), in some circumstances cells can recover following executioner caspase activation, in a process termed anastasis (Sun & Montell 2017), described further below.

Elimination of specific cells by apoptosis is critical for regulating cell numbers, sculpting tissues, and eliminating unwanted cells throughout animal development and adulthood. Classic examples of developmental apoptosis include removal of interdigital webs during limb formation, metamorphosis of the endocardial cushion into cardiac valves and septa, and elimination of surplus neurons (Abdelwahid et al. 2002, Dekkers et al. 2013, Fisher et al. 2000, Lindsten et al. 2000). Apoptosis also protects tissues by removing potentially harmful cells. For example, in the immune system, self-reactive lymphocytes are removed in the thymus by apoptosis to avoid their release into the circulation, which could lead to autoimmune reactions (Feig & Peter 2007). The apoptotic program also removes cells with unrepaired DNA damage (Roos et al. 2015), which is important for tumor suppression. Additionally, apoptosis suppresses lymphomas and carcinomas by promoting the homeostatic turnover of cells such as B cells and epithelial cells, respectively. Genetic rearrangements that cause overexpression of the apoptosis-inhibiting *Bcl2* gene cooperate with oncogenes to cause B cell lymphomas by delaying or preventing the normal turnover of these cells by apoptosis (Yip & Reed 2008). Moreover, *p53*, a critical promoter of apoptosis in cells with DNA damage, is the most commonly mutated gene in human cancer (Muller & Vousden 2013). Additionally, tumor cells can induce apoptosis in tumor-reactive T cells by expressing programmed death ligand 1 (PDL1), thus suppressing the antitumor immune response (Dong et al. 2002). Apoptosis is, therefore, a biochemically well-defined process essential for normal development and homeostasis and plays complex roles in both causing and preventing disease.

Death by Extrusion and Anoikis

Cells within epithelia turn over at some of the fastest rates in the body, which may be why these are the tissues where most cancers arise. How do tissues match the numbers of cells that are dividing with those that are dying? Epithelia match the number of cells that divide with the number that die through mechanical force: When epithelial cells become too crowded, they extrude live cells that then die by anoikis (Eisenhoffer et al. 2012). Additionally, when cells within a monolayer are triggered to undergo apoptosis, they are extruded as they die (Andrade & Rosenblatt 2011, Rosenblatt et al. 2001). To extrude, both live and dying cells produce and emit the bioactive lipid sphingosine-1-phosphate (S1P), which binds the G protein–coupled receptor sphingosine-1-phosphate receptor 2 ($S1P_2$) in their neighboring cells to activate Rho-mediated contraction of an actomyosin ring (Gu et al. 2011, Slattum et al. 2009). Actomyosin contraction squeezes live cells apically out of the epithelial monolayer, while neighboring cells move in to prevent a gap from forming, thus preserving epithelial barrier function). While apoptotic stimuli can simultaneously activate apoptosis and extrusion, during homeostatic turnover mechanical crowding activates the stretch-activated channel Piezo1 to activate live cell extrusion (Eisenhoffer et al. 2012). Once live cells extrude, they then die by anoikis because they are stripped from the matrix and neighboring cells that provide them with survival signals. In this way, cells are killed by their neighbors through extrusion to maintain constant cell numbers. In contrast, during *Drosophila* development, cells extrude basally (such extrusions are also termed delaminations) and die as a result of proapoptotic signaling, rather than loss of survival signals (Meghana et al. 2011, Levayer et al. 2016). Oncogenic mutations can disrupt the apical extrusion pathway, leading to cell masses at sites where cells would normally have

extruded, underscoring the importance of apical extrusion in maintaining constant epithelial cell densities and suppressing tumor formation (Gu et al. 2015, Marshall et al. 2011, Slattum et al. 2014).

Autophagic Cell Death

Autophagy is a conserved catabolic process that degrades cellular contents and recycles damaged organelles (Kroemer et al. 2010, Takeshige et al. 1992). During autophagy, cells form autophagosomes that capture cellular contents and target them for degradation (Nakatogawa et al. 2009, Takeshige et al. 1992). By blocking growth signaling and promoting autophagosome formation, autophagy typically regulates protein levels and promotes survival in cells experiencing nutrient insufficiency and other types of stress. The molecular mechanism of autophagy requires several conserved Atg (autophagy-related) proteins and comprises three main steps: initiation, nucleation, and elongation (Kaur & Debnath 2015). Autophagosome formation is initiated by phagophore (or isolation membrane) assembly by the ULK1 complex and nucleation by the class III phosphatidylinositol kinase (PI3K)-Beclin1 (yeast Atg8) complex. Elongation and formation of the autophagosome require two ubiquitin-like conjugation systems. The Atg12-Atg5-Atg16 complex promotes lipidation of the microtubule-associated protein 1 light chain 3 (LC3) with phosphatidylethanolamine (PE) to form the LC3-II complex, which elongates the membranes of the forming autophagosome. The LC3-II complex remains covalently bound to the mature autophagosome until it fuses with the lysosome to form an autolysosome. Lysosomal hydrolases degrade the contents of the autolysosome, including internalized LC3, so that molecules, particularly amino acids, can be released into the cytosol to serve as building blocks to conserve energy and rebuild organelles (White 2012). However, components of the autophagic machinery can also kill cells (Bursch 2001). Large cytosolic autophagic vacuoles from accumulated autophagosomes, marked by LC3 labeling, are the most observable characteristics of ACD (Galluzzi et al. 2015). The mechanisms regulating ACD are not well understood, although the emerging roles of proapoptotic factors AMPK, MAPK, BNIP3, and cathepsin L in ACD suggest that there is likely cross talk between autophagy and apoptosis (Liu & Levine 2015). It is likely for this reason that the term autophagic cell death is under debate. Currently, the term ACD should be used only in cases in which cell death (*a*) occurs independently of apoptosis, (*b*) shows increased autophagic flux (not just increased autophagic markers), and (*c*) is suppressed by inhibition or knockdown of essential autophagic proteins (Denton et al. 2012, Galluzzi et al. 2015).

Physiologically, ACD plays roles in *Dictyostelium* and *Drosophila* development. *Dictyostelium discoideum* lacks caspases and Bcl-2 family proteins. Starvation of this organism triggers single cells to aggregate into a multicellular structure that undergoes differentiation into stalk cells and spores. Stalk cells undergo Atg1-induced autophagy, which, together with a second signal, the differentiation inducing factor-1 (DIF-1) (Kay 1987, Morris et al. 1987), eventually leads to stalk cell death. Thus, the DIF-1 signal converts autophagy into ACD (Giusti et al. 2009). Developmental ACD has also been characterized in *Drosophila* during salivary gland and midgut development (Tracy & Baehrecke 2013). Even though flies have an intact apoptotic machinery, cell death in the midgut occurs primarily through ACD (Denton et al. 2009). In contrast, destruction of the

salivary gland requires both caspase activity and autophagy pathways (Berry & Baehrecke 2008).

In mammals, thus far, ACD has been reported only in cells with mutations in normal cell death pathways. For instance, ACD may be an important alternative death pathway for tumor cells with oncogenic Ras^{V12} mutations that amplify autophagy for survival. Dying Ras mutant cells do not activate caspases or other apoptotic markers but do express Beclin, a central regulator of autophagy (Elgendy et al. 2011). Additionally, mouse embryonic fibroblasts deficient in proapoptotic Bax and Bak1 or multiple myeloma cells deficient in caspase-10 activity undergo Beclin-1-and Atg5-dependent autophagic death (Lamy et al. 2013, Shimizu et al. 2004). Thus, ACD appears to serve as a backup death program when apoptosis is insufficient or inhibited. Thus, certain cancer cells may be more vulnerable than normal cells to ACD, opening an avenue to exploit for treatment.

Finally, autosis represents a distinct cell death mechanism that is similar to ACD. Autosis is morphologically characterized by the disappearance of the endoplasmic reticulum and by convolution and swelling of the perinuclear space (Liu et al. 2013). Disruption of a Na^+, K^+-ATPase protects a variety of cell types from experimental induction of autosis (Liu & Levine 2015), suggesting that the ATPase function promotes autosis, but the mechanism still remains mysterious.

Cultured cells that are starved or exposed to a Beclin1-derived peptide, neurons in cerebral ischemia, and hepatocytes of patients with severe anorexia nervosa exhibit hallmarks of autosis (Kheloufi et al. 2015, Liu et al. 2013, C. Xie et al. 2016).

Necrosis

Necrosis, defined by cellular swelling and rupture of the plasma membrane, is the most common form of accidental cell death, typically in response to severe cellular, chemical, or physical stress (Vanlangenakker et al. 2012). Necrosis can also result when apoptotic cells are not phagocytosed after undergoing apoptosis, in a process termed secondary necrosis (Silva et al. 2008). In contrast to apoptosis, which can eliminate numerous cells without causing inflammation, necrosis activates an inflammatory response. Interestingly, secondary necrosis is no accident but rather is controlled by a specific biochemical pathway. Caspase-3 regulates secondary necrosis by cleaving DFNA5 (deafness-associated tumor suppressor), which converts it into a necrosis-promoting DFNA5-N fragment (Rogers et al. 2017). The DFNA5-N fragment inserts into the plasma membrane, forming a large pore that releases inflammatory molecules (Rogers et al. 2017). Additional forms of regulated necrosis include necroptosis, pyroptosis, and ferroptosis, each of which is briefly summarized below (Table 1).

UNCONVENTIONAL FORMS OF CELL DEATH

Necroptosis

The best-characterized form of regulated necrotic cell death is necroptosis, a pathway important in inflammation and viral infection (Ashkenazi & Salvesen 2014, Weinlich et al. 2017). Necroptosis requires activation of the receptor-interacting kinases 1 and 3 (RIPK1

and −3) (Cho et al. 2009, Zhang et al. 2016), which results in the phosphorylation of the pseudokinase mixed lineage kinas-like (MLKL), causing its oligomerization and activation (Grootjans et al. 2017, Sun et al. 2012). Active MLKL then localizes to intracellular and plasma membranes, where it disrupts membrane integrity to kill the cell (Cai et al. 2013, Wang et al. 2014). Plasma membrane breakdown causes necroptotic cells to release damage-associated molecular patterns (DAMPs) important for activating the inflammatory pathway (Kaczmarek et al. 2013). During viral infection, necroptosis can act as a backup death pathway when viral proteins inhibit caspases. Mice lacking RIPK3 are more susceptible to viral and *Yersinia* infection (Jorgensen et al. 2017, Kaiser et al. 2013). However, necroptosis is not always beneficial. Some viruses and bacteria can induce immune cell necroptosis, resulting in reduced pathogen control and inflammation (Weinlich et al. 2017). Necroptotic death may also have important roles in cancer. Necroptosis of endothelial cells, for example, can promote tumor extravasation facilitating metastasis, and low MLKL expression is correlated with poor prognosis of patients with gastric and cervical cancers (Ertao et al. 2016, Grootjans et al. 2017, Ruan et al. 2015, Strilic et al. 2016).

Pyroptosis

Pyroptosis is an essential antimicrobial response that triggers a cell-autonomous inflammatory form of regulated cell death in response to bacteria, viral, fungal, and protozoan infections (Cookson & Brennan 2001, Man et al. 2017). A set of caspases distinct from those used in apoptosis—caspase-1, human caspase-4, human caspase-5, and mouse caspase-11—activate the pyroptotic pathway in response to formation of an inflammasome (Man et al. 2017). The inflammasome is a multiprotein complex formed by activation of pattern recognition receptors like the Nod-like receptors (NLRs) (Bergsbaken et al. 2009). The inflammasome-activated caspases then cleave the propyroptotic protein Gasdermin D (GSDMD), which forms a pore in the plasma membrane and causes cell lysis (He et al. 2015, Liu et al. 2016). Interestingly, some chemotherapy drugs can increase inflammasome activity, which could potentially help mobilize the body’s own immune response to a tumor (Thi & Hong 2017). Thus, promoting pyroptosis over apoptosis of tumors is an important new line of investigation for cancer therapy (Kolb et al. 2014).

Ferroptosis

Ferroptosis, an iron-dependent form of regulated cell death (Y. Xie et al. 2016), was first discovered in cancer cells treated with erastin, a VDAC2 and VDAC3 inhibitor that selectively targets the oncogenic form of RAS (Dixon et al. 2012). Here, metabolic dysfunction causes iron-dependent reactive oxygen species (ROS) accumulation to promote cell death (Dixon et al. 2012). Reduction of the antioxidant glutathione or direct inhibition of glutathione peroxidase 4 leads to the accumulation of ROS, which activates ferroptosis (Yang et al. 2014). In an effort to overcome apoptotic resistance and improve drug efficacy, researchers are now identifying drugs that induce ferroptotic death in cancer cells (Ma et al. 2016, Zhu et al. 2017). Ferroptosis has thus far been identified only in drug therapy responses, so whether it plays a role in normal physiology is not clear. Its therapeutic value may be greatest if it does not play a role in normal physiology, by limiting possible side effects.

Phagoptosis and Entosis

Phagoptosis is a form of cell murder that occurs when a phagocyte consumes an otherwise viable cell (Brown & Neher 2012). This process is distinct from phagocytosis of apoptotic or necrotic cells. Yet, similarly to phagocytosis, cell surface exposure of the eat-me signal, phosphatidylserine, and/or loss of the don't-eat-me signal CD47 is critical for phagoptosis (Brown & Neher 2012). The mechanisms that regulate phagoptosis are yet to be fully understood.

Physiologically, phagoptosis is responsible for erythrocyte and neutrophil turnover and, thus, may represent the most common death program used in the body (Brown & Neher 2012). However, phagoptosis also has pathological roles. For instance, neuroinflammation can cause microglia to kill viable neurons by phagoptosis, possibly leading to neuronal degeneration (Neher et al. 2012). In contrast, human cancer cells can avoid phagoptosis by upregulating CD47 on their surfaces (Willingham et al. 2012).

In contrast to phagoptosis, entosis occurs when a live cell drives itself inside another cell, rather than passively being eaten (Overholtzer et al. 2007). Entosis does not require phosphatidylserine exposure. Rather, the entosing cell requires adherens junction proteins, ROCK activity, and actomyosin contractions to physically force its way into an adjacent cell (Overholtzer et al. 2007). Following entosis, the internalized cell has three different fates: cell death, cell division, or exit). Internalized cells are surrounded by an entotic vacuole membrane that recruits LC3, a component of autophagosomes (Florey et al. 2011). The LC3-targeted entotic vacuole membrane then recruits lysosomes to degrade the internalized cell, resulting in death of the entosed cell (Florey et al. 2011).

Entosis has also been noted in mice to remove cells within the epithelial barrier during normal implantation (Li et al. 2015). Furthermore, soft agar assays suggest that entosis may inhibit tumor growth, as the inhibition of entosis increases colony formation (Overholtzer et al. 2007, Sun et al. 2014). Thus, entosis may function as an additional mechanism to eliminate matrix-detached cells.

Other Forms of Cell Death

Oher forms of unconventional cell death remain the subject of active research, and the list is likely to continue to grow. Here, we briefly mention a few types, indicating where to find more information. Cornification is a form of programmed cell death specific to outer epidermal keratinocytes, where dead cell layers remain attached to live layers to provide a thicker protective barrier until the former are eventually sloughed off from the skin (Eckhart et al. 2013). Parthanatos is a form of regulated necrosis caused by PARP-1 overactivation during traumatic brain injury, excitotoxicity, and ischemia and in many neurodegenerative disorders (Fuchslocher Chico et al. 2017). NETosis is a form of pathogen-induced neutrophil death, which causes release of NETs (neutrophil extracellular traps) made of DNA following cell lysis (Remijsen et al. 2011). Here, the DNA forms massive nets that bind and capture more pathogens to aid the immune response. In male *Caenorhabditis elegans* larvae, a single cell, termed the linker cell, migrates from the middle of the larva to the posterior cloaca, pulling the gonad along behind it, and then dies through a cell-autonomous, nonapoptotic

process termed linker cell death (Abraham et al. 2007, Malin et al. 2016). During *Drosophila* oogenesis, support cells termed nurse cells die after contributing most of their cytoplasm to the developing oocyte. This physiological death incorporates morphological and biochemical elements of apoptosis, necrosis, and phagoptosis of the germline nurse cells by the somatic follicle cells (Peterson et al. 2015). When female flies are starved or otherwise stressed, they activate these mechanisms earlier during egg development to recoup nutrients and limit energy expenditure. The relatively large size of the polypoid nurse cells may engender the need to mobilize multiple death pathways to eliminate them.

The diversity of death mechanisms described above presents a challenge if the goal is to enhance or block all cellular demise. But this same diversity might offer opportunities if the goal is selective cell killing or rescue. If all cells died by the same mechanism, it would be difficult to kill tumor cells without harming beneficial cells. The diversity of death mechanisms may allow for identification of specific vulnerabilities of cancer cells while fostering the health and well-being of tissue stem cells, cardiomyocytes, and neurons. Furthermore, appreciating the diversity of mechanisms by which harmful cells can die may reveal strategies to trigger alternate cell death pathways if canonical death components are disabled by mutation or by other means. Next, we discuss mechanisms that cells have evolved to escape death in both normal physiology and disease.

RECOVERY FROM THE BRINK OF DEATH

Earlier work suggested that cells commit irreversibly to death once they cross a biochemically defined point of no return. However, recent studies show that multiple cell types can reverse and survive biochemical hallmarks of apoptosis, entosis, and necroptosis (Figure 1, Table 2). Here, we describe examples in which cells can survive near-death experiences.

Anastasis: Cell Survival Following Apoptotic Activation of Caspase-3

Caspase-3 activation was widely considered a point of no return in terms of activation of apoptosis, yet recent findings show that this is not the case. A variety of cultured mammalian cells, including primary cells, cell lines, and cancer cells, can survive caspase-3 activation by using a process termed anastasis, a Greek word meaning rising to life (Sun & Montell 2017, Tang et al. 2012). Anastasis occurs when cells are treated with potentially lethal doses of chemicals such as ethanol, DMSO, or staurosporine but survive, if the treatment is transient. Cells at the brink of chemically induced apoptosis show classic morphological signs such as shrinkage and blebbing, as well as biochemical hallmarks such as phosphatidylserine exposure and caspase-3 activation. If left in the toxins, the treated cells die. However, if the inducer of cell death is removed, most of the treated cells recover normal morphology, survive, and divide (Figure 1).

RNAseq of mammalian cancer cells undergoing anastasis has revealed two discrete phases, with different sets of genes transcribed during the first 4 h compared to the next 8 to 12 h of recovery (Sun et al. 2017). Strikingly, some mRNAs that are highly induced 1 h following removal of the apoptotic stimulus are already enriched in cells on the brink of apoptotic death. For example, the mRNA encoding the zinc-finger transcription factor Snail is

enriched but not translated in cells treated with a potentially lethal dose of EtOH for 3 h. Once the EtOH is washed out, Snail mRNA is translated, which is required for anastasis (Sun et al. 2017).

Discovery of factors critical for anastasis could have important implications in disease. Radiation and chemotherapy for cancer induce apoptosis but are delivered transiently, due to their toxicity. Therefore, if even a fraction of tumor cells undergo anastasis in vivo during or after treatment, they could sow the seeds for relapse. Survival from caspase activation can also result in genetic instability and oncogenic transformation, suggesting that anastasis may contribute to tumor initiation (Cartwright et al. 2017, Liu et al. 2015, Pérez et al. 2017, Tang et al. 2012). In addition, HeLa cells that undergo anastasis first proliferate and then increase motility (Sun et al. 2017) (Figure 1), properties associated with tumor progression, raising the possibility that anastasis contributes to tumor initiation, progression, and/or relapse following therapy.

In contrast to the potentially harmful consequences of anastasis in cancer, in normal cells, especially those that are difficult to replace such as neurons or cardiomyocytes, anastasis could help preserve cells following transient injury. In support of this idea, cardiomyocytes appear to undergo anastasis in vivo following transient ischemia (Kenis et al. 2010). In another example, in a mouse model of tau-mediated neurodegeneration, overexpression of a mutant form of human tau protein triggers caspase-3 activation in neurons. Simultaneous live imaging of caspase-3 activity and tau tangles in the brains of these mice shows that cells with transient caspase activity can survive long term (de Calignon et al. 2010). While caspase-3 activation precedes tangle formation, the precise relationship between caspase-3 and tangles is not clear. The observation that the neurons survive caspase-3 activation, however, suggests that they may represent another example of in vivo anastasis, in the context of neurodegenerative disease.

Another example of in vivo anastasis is the surprising discovery of developmental anastasis (Ding et al. 2016), which occurs in rapidly growing *Drosophila* epithelia. A particularly clear example is found in the developing pupal notum, where live imaging reveals that mechanical crowding leads to caspase-3 activation in a subset of cells, only some of which go on to die by apoptosis (Levayer et al. 2016). This finding is consistent with the idea that, rather than a single, all-or-none event, different rates and levels of caspase-3 activation likely influence whether a cell ultimately dies or retains the capacity to recover.

In a possibly related process, when a limited population of mitochondria permeabilize in a process termed minority MOMP, sublethal caspase activation occurs, promoting transformation and tumorigenesis (Ichim et al. 2015). However, minority MOMP does not cause sufficient caspase activation to result in the morphological hallmarks of apoptosis. Therefore, while both anastasis and minority MOMP can lead to survival of cells with DNA damage and oncogenic transformation, additional work is required to establish the mechanistic similarities and differences.

Resuscitation: Reversing Necroptosis

Human colon cancer cells (HT-29 cells), NIH3T3 cells, and Jurkat cells can reverse and survive necroptosis in a process termed resuscitation (Gong et al. 2017b, Zargarian et al. 2017). By controlling the activity of RIPK3 and MLKL, survival following necroptosis has been observed upon chemical inactivation of RIPK3 or MLKL (Gong et al. 2017b). These cells use ESCRT-III-mediated membrane repair to survive MLKL activation and plasma membrane disruption (Gong et al. 2017b) (Figure 1). Recent work has reported that MLKL itself can regulate endosomal trafficking and extracellular vesicle generation (Yoon et al. 2017). Interestingly, this function of MLKL is RIPK3 independent and can result in the release of phosphorylated MLKL withholding necroptotic death (Yoon et al. 2017).

Both anastasis and resuscitation are processes that reverse cell death programs. To compare these processes at the molecular level, transcriptomes of cells undergoing anastasis versus resuscitation were evaluated. From this analysis, the processes appear to be mostly distinct, with the caveat that the transcriptomes are derived from different cell types (Gong et al. 2017a). Although there were more differences than similarities, both resuscitation and anastasis signatures show upregulated FGFR1, highlighting mitogenic signaling during both types of recovery (Gong et al. 2017a). Further research into the unique data sets will undoubtedly reveal new information about the mechanisms that control each of these processes and how they might be exploited therapeutically.

Autophagy as a Survival Mechanism in Normal Physiology

Although cells can die by ACD, the main function of autophagy is to promote cell survival during normal tissue homeostasis. The prosurvival function of autophagy is conserved from yeast to humans and plays an important role in adaptive metabolic responses to a variety of stresses, including nutrient deprivation, growth factor withdrawal, hypoxia, and infection (Kroemer et al. 2010). When cells lack essential nutrients, autolysosomal degradation of membrane lipids and proteins provides free macromolecules that can be reused to generate energy and sustain protein synthesis (Rabinowitz & White 2010). This recycling function of autophagy can preserve life during starvation. For example, in the mammalian liver, autophagy is activated during nutrient deficiency to produce glucose from amino acids to provide nutrients to the brain and erythrocytes (Ezaki et al. 2011).

In addition to autophagy playing a role in adaptive responses, basal levels of autophagy are seen in many cell types independently of nutrient status or stress. For example, in liver cells, selective turnover of specific cargos contributes to the basic hepatic functions of glyconeogenesis, gluconeogenesis, and β-oxidation (Singh et al. 2009). Basal autophagy helps maintain muscle mass and myofiber integrity, which protects against stress-induced muscle degeneration (Finn & Dice 2006). Autophagy also serves an essential quality control function in cells by supporting nonselective turnover of cytoplasmic content and selective removal of damaged organelles such as mitochondria, large protein aggregates, and intracellular pathogens. In this way, autophagy promotes cell survival during aging or disease states (Kraft et al. 2010). However, autophagy also plays key roles in several pathological conditions, and its role in cancer progression can be especially complex, as described below.

DYSREGULATION OF CELL DEATH AND SURVIVAL IN CANCER

Autophagy

Relative to normal cells, tumor cells can have high metabolic needs and experience oxygen and nutrient deficiencies as they enter new microenvironments, so enhancing autophagy can enable their survival (Rabinowitz & White 2010). For example, tumors experiencing hypoxia can stimulate adaptive autophagy through hypoxia-inducible factor 1 alpha (HIF1-α)-dependent activation of proapoptotic proteins that induce autophagy without triggering cell death (Mazure & Pouysségur 2009). Similarly, under nutrient deprivation conditions, AMP kinase activates catabolic autophagy, which provides nutrients required for tumor survival (Kim et al. 2011).

Oncogenic mutations in K-Ras are common in a large percentage of poor-prognosis tumors, including lung, colon, and pancreatic cancers. Ras-driven cancers are notably addicted to autophagy, a process that likely promotes growth of the primary tumor, as well as survival after invasion, essential for metastasis (Guo et al. 2011, 2013; Lock et al. 2014; Yang et al. 2011). Expressing *K-Ras*^{G12V} or *H-Ras*^{G12V} activating mutations is sufficient to upregulate autophagy in cultured cells. Indeed, autophagy deficiency reduces growth of *K-Ras*^{G12V}-driven non–small cell lung carcinomas in genetically engineered mouse models (Guo et al. 2013). Autophagy deficiency actually diverts the tumors from adenomas and carcinomas to benign oncocytomas (Guo et al. 2013). These studies have suggested that blocking autophagy using chloroquine, an established antimalarial drug, could hold promise in treating these cancers. Clinical trials are under way to test this possibility (Manic et al. 2014).

Entosis

Entosis appears frequently in cancer, with a third of the cells in breast cancers showing internalized live cells (Kroemer & Perfettini 2014, Overholtzer et al. 2007). Because the fate of an entosed cell can vary (Figure 1), entosis may either suppress or promote tumor formation. Entosis may act as a tumor suppressor by internalizing and killing abnormally dividing cells and may account for another mechanism by which E-cadherin expression yields a better prognosis for tumors, since it is needed for entosis (Durgan et al. 2017, Sun et al. 2014) (Figure 1). However, entosis can also promote tumor formation, as entosed cells can interfere with cytokinesis of the host cell, leading to aneuploidy (Krajcovic et al. 2011). Entosed cancer cells may be able to survive and proliferate inside another cell during metabolic stress and starvation—conditions commonly seen in tumors. Entotic cell cannibalism also requires autophagic LC3 and lysosomal LAMP1, which could similarly release the contents of the digested entosed cell into the host cell, amplifying the latter cell's survival (Florey et al. 2011). Under such circumstances, autophagy may act as a potential mechanism to allow wild-type cells to acquire the tumorigenic properties of the entosed cancer cell, essentially non–cell autonomously spreading the tumor. Alternatively, entosis could allow tumor cells to internalize and replace wild-type cells and thus support tumor progression. Tumor cells are known to escape immune surveillance by a variety of mechanisms (Vinay et al. 2015). A large-scale survey of different cell types showed that heterotypic cell-in-cell structures are formed between a variety of tumor cell lines and

immune cells, perhaps as a mechanism to escape immune attack (Chen et al. 2013). Entosed tumor cells can also emerge to live autonomously again (Figure 1). At this point, while entosis is a frequent hallmark in tumor pathology, what is not yet clear is whether it represents a way for the body to remove neoplastic cells or a way for tumors to spread and hide from the immune system. It is likely, as with many aspects of cancer, that both processes occur, thus limiting some cancers while promoting others.

Resisting Anoikis

Anoikis is an indispensable mechanism for maintaining tissue homeostasis by preventing cells from surviving at sites where they do not belong. Thus, resistance to anoikis is a critical step for tumor cell invasion (Frisch et al. 2013, Hanahan & Weinberg 2011) and metastasis (Kim et al. 2012, Simpson et al. 2008) (Table 2). Cancer cells deploy several mechanisms to achieve anoikis resistance. Aside from using autophagy in response to metabolic stress to promote survival and resistance to anoikis (Fung et al. 2008), many aggressive cancers have adopted differential signaling to bypass anoikis and survive in places that normal cells cannot.

Many cancer cells aberrantly activate protein tyrosine kinases (PTKs) to escape anoikis (Gschwind et al. 2004), making them attractive targets for therapy. In particular, upregulation of epidermal growth factor receptor (EGFR) families plays an important role in overriding anoikis. Mammary epithelial cells that fail to grow on surfaces lacking ECM have reduced EGFR levels and increased levels of the proapoptotic protein Bim (Debnath et al. 2002, Reginato et al. 2005). Cancer cells that override anoikis, however, compensate for EGFR loss by either overexpressing ERBB2 (a member of the EGFR family) or activating the proto-oncogene Src, both of which suppress apoptosis by activating the ERK/MAPK pathway (Reginato et al. 2005). Additionally, ERBB2 can enable cell survival by stabilizing EGFR and β1 integrin, which usually degrade upon ECM detachment (Grassian et al. 2011). ERBB2 can also promote cell survival by upregulating α5 integrin, which activates Src (Haenssen et al. 2010) through regulation of HIFs (Whelan et al. 2013). Misregulated expression of another PTK, the insulin-like growth factor 1 receptor, can also promote anoikis resistance by activating the PI3K/AKT pathway (Chen & Sharon 2013, Dunn et al. 1998, Resnicoff et al. 1994). Other mechanisms of anoikis suppression include transforming growth factor β (TGF-β)-activated kinase 1–mediated WNT2 signaling in pancreatic circulating tumor cells (Yu et al. 2012) and stimulation of integrin-linked kinase activity in breast cancer cells (Attwell et al. 2000, Weigel et al. 2014).

Oncogenic mutations in K-Ras, HRas, or NRas not only increase autophagy, as described above, but also can upregulate survival signaling by constitutively activating PI3K/AKT signaling (Castellano & Downward 2011), upregulating antiapoptotic Bcl-X_L (Rosen et al. 2000), or downregulating caspase-2 (Yoo et al. 2011). Mutations in Raf kinases, downstream effectors of Ras, also promote survival upon matrix detachment through activation of PI3K or ERK pathways (Boisvert-Adamo & Aplin 2006). Moreover, in cases in which extrusion signaling is inhibited, the lack of cell detachment from the matrix results in upregulation of focal adhesion kinase (FAK)—a kinase that is now being targeted in clinical trials of many cancers—and in chemotherapy resistance (Gu et al. 2015).

In contrast, Rho protein overexpression, seen in many human tumors, can have both positive and negative effects on anoikis (Sahai & Marshall 2002). RhoG suppresses anoikis in HeLa cell lines in a PI3K-dependent manner (Yamaki et al. 2007). Yet RhoA and AKT prevent anoikis by activating FAK in B16F10 melanoma cells (Goundiam et al. 2012), and RhoA suppression in KRas-driven lung tumors also blocks anoikis (Ma et al. 2007). Therefore, there may be discrepancies regarding RhoA roles in tumor cell survival, depending on the type of tumor or whether the studies are done in vivo or in culture. Another possibility is that Rho overrides anoikis by changing the identity of the tumor cell, rather than merely its survival. An example is the epithelial-tomesenchymal transition (EMT), in which polarized epithelial cells adopt a mesenchymal phenotype with increased migration, invasiveness, and resistance to apoptosis. During EMT, loss of E-cadherin, activation of TGF-β signaling via the transcription factors Twist and Snail, and N-cadherin expression can lead to anoikis resistance and increased tumor invasiveness (Araki et al. 2011, Derksen et al. 2006, Diamond et al. 2008, Lamouille et al. 2014, Yang et al. 2004).

Basal Extrusion

For epithelia to maintain a constant barrier in the face of high rates of cell death and division, cells fated to die are first extruded by concerted contraction of their neighboring cells. When cells extrude, the direction in which the cell extrudes determines its fate. Typically, in vertebrates, cells extrude apically into a lumen (Figure 2). Because the apically extruded cells detach from the matrix, which provides survival signaling, they die by anoikis. Extrusion is the chief mechanism by which epithelial cells apoptose, and thus extrusion may be thought of as tumor suppressive. However, in some instances, cells can extrude basally beneath the epithelial sheet (Figure 2), allowing them to take on different fates.

A class of oncogenic mutations (in K-Ras, APC, and $S1P_2$) that drive aggressive, invasive cancers can hijack the apical extrusion pathway, causing cells normally fated for apoptosis to either accumulate in masses or extrude basally (Table 2, Figure 2). Basal extrusion of transformed cells may enable invasion and metastasis to other sites in the body. Each of these mutations appears to target different key signals in the apical extrusion pathway: APC truncation mutations disrupt S1P trafficking to neighboring cells (Marshall et al. 2011); unknown mechanisms in pancreatic, lung, and colon cancer epigenetically downregulate the $S1P_2$ receptor essential for extrusion (Gu et al. 2015); and $K\text{-}Ras^{G12V}$ causes lysosomal degradation of S1P through increased autophagy (Slattum & Rosenblatt 2014, Slattum et al. 2014). Additionally, in $K\text{-}Ras^{G12V}$-driven pancreatic intraepithelial neoplasia mouse models, biallelic loss of the adherens junction protein P120 catenin causes extensive extrusion, both apically and basally (Hendley et al. 2016). The growing list of driver mutations of aggressive, invasive cancers that disrupt canonical apical extrusion suggests that extrusion is important not only for promoting apoptosis but also for preventing tumor invasion. Additionally, it suggests that epithelial cells expelled basally into the stroma may encounter enough survival signaling to avert anoikis or to change fate so as to become independent of the ECM for survival, as suggested above for EMT.

SUMMARY AND OPEN QUESTIONS

The discovery of programmed cell death pathways in normal development and disease, followed by the elucidation of biochemical and genetic mechanisms, raised hopes that antitumor therapies based on promoting tumor cell apoptosis would soon follow. The complexities described here—multiple cell death pathways and the capacity of cells to resist death or recover from the brink of death—are one reason that therapies activating the core apoptosis machinery have limitations. Globally targeting canonical apoptotic mechanisms may not only fail to kill all tumor cells but may also eliminate beneficial cells, such as tumor-reactive T cells. The most recent successes in cancer therapy establish that selective cell killing is key. The power of anti-PDL1 therapy is that it enhances the immune response to tumors by rescuing tumor-reactive T cells from tumor-induced programmed cell death. This success underscores the importance of seeking therapies with better specificity, i.e., selectively targeting harmful cells while protecting beneficial cells.

We may be just beginning to understand the multifaceted tug of war between cell death and survival. Many questions remain unanswered. For example, under physiological conditions, how are only some types of cells targeted to die, and what protects surrounding cells? What sets the rate of turnover in different tissues? How does the microenvironment influence homeostatic cell death, and how do tumor cells manage to survive under these conditions? What are the true points of no return, if any, in the various cell death programs? What are the mechanisms by which cells reverse death processes to survive? Understanding how cell death and survival processes are controlled and intersect normally may yield insights into their roles in cancer and into the development of effective and cell type–specific combination therapies.

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SUMMARY POINTS

1. In addition to apoptosis, ACD, anoikis, and necrosis, unconventional, biochemically distinct forms of cell death have been discovered. These include regulated forms of necrosis, including pyroptosis, necroptosis, ferroptosis, and parthanatos, as well as cornification, NETosis, linker cell death, phagoptosis, and entosis.
2. Apical extrusion is an important mechanism that protects epithelial barrier function by removing apoptotic cells and preventing gaps in the epithelium. Importantly, extrusion also drives cell death during normal epithelial turnover. When epithelial monolayers become too crowded, they extrude live cells that go on to die by anoikis, which is a specific form of apoptosis.
3. Cells can recover from the brink of apoptotic cell death, even after executioner caspase activation, in a process termed anastasis, which is a Greek term meaning rising to life.
4. Necroptosis is an important immune-promoting cell death response, but its activation by RIPK3 and MLKL is not always sufficient to kill a cell. ESCRT-III complexes can act with MLKL to repair and maintain plasma membrane integrity, allowing for cell survival in a process termed necroptosis resuscitation.
5. The prosurvival function of autophagy is essential for homeostatic turnover of selective cargo and for metabolic response to a variety of stresses. However, tumor cells that have high metabolic needs upregulate adaptive autophagy to survive transient oxygen and nutrient deficiencies as they move to new microenvironments.6. Anoikis is an important mechanism to prevent cells from surviving at sites where they do not belong. Thus, resistance to anoikis is a critical step for tumor cell invasion, and many aggressive cancers adopt differential signaling mechanisms to override anoikis and to survive in places where normal cells cannot.
6. Because extrusion is the chief mechanism by which epithelial cells die, extrusion can be considered a tumor-suppressive mechanism. However, basal extrusion can permit survival. Oncogenic mutations that drive aggressive cancers can hijack the homeostatic apical extrusion pathway, override anoikis, and allow cells to accumulate in masses or escape by extruding basally and to survive.

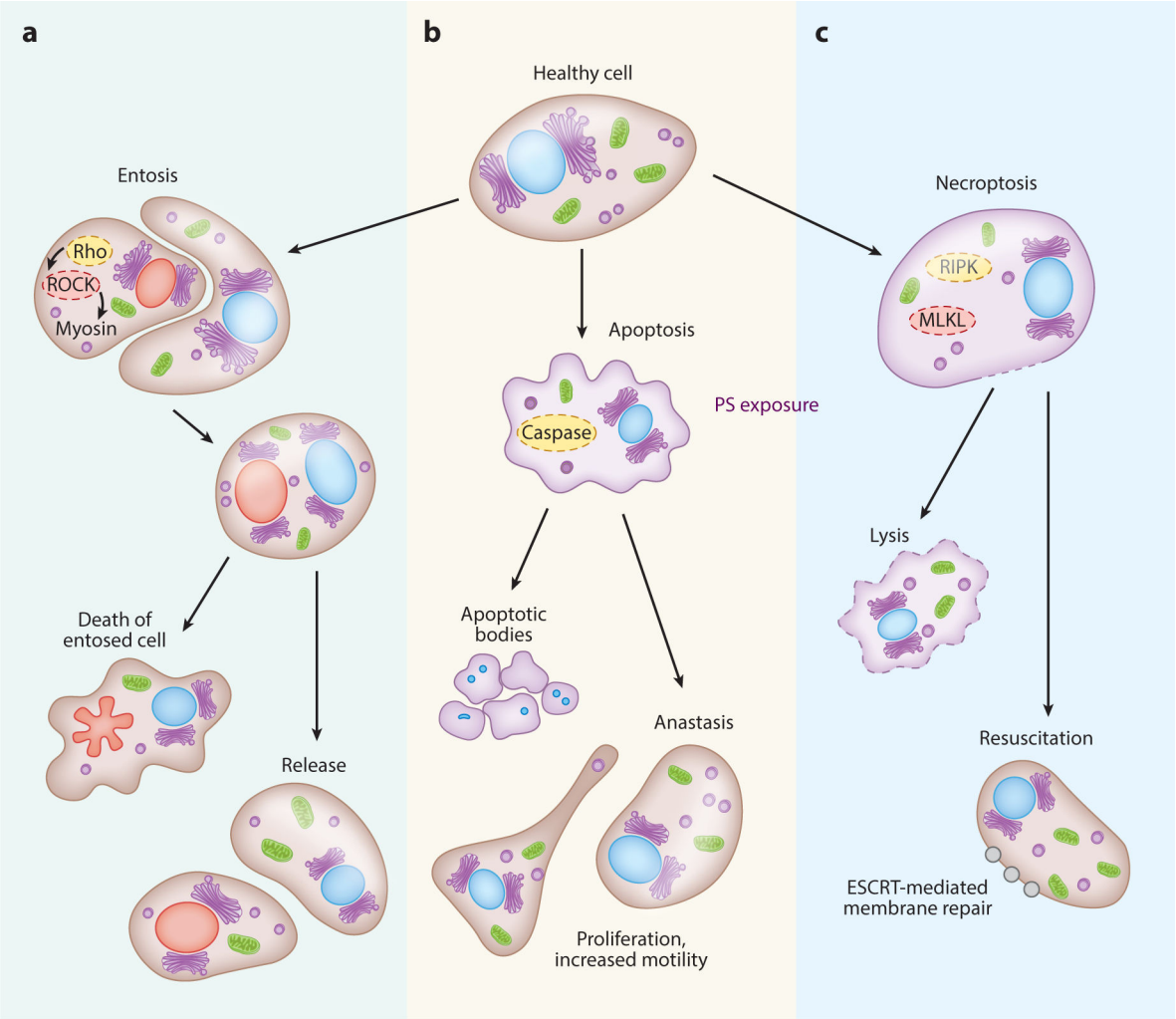

Figure 1.

Recovery from the brink of death. Eukaryotic cells have been reported to survive the biochemical hallmarks of entosis, apoptosis, and necroptosis. (*a*) Entosis results when one cell pushes itself into another by Rho- and ROCK-driven myosin contraction. This results in a cell-in-cell structure. The entosed cell, whether a cancer cell or a normal cell, can either be degraded within the host cell or be released and survive. (*b*) Apoptosis results in cell shrinkage, membrane blebbing, and phosphatidylserine (PS) exposure (*purple*) due to executioner caspase activation. Cells with activated caspase can break into apoptotic bodies and die or can undergo anastasis and recover. Survival by anastasis can result in an elongated cell morphology and increased motility. (*c*) Necroptosis is a form of regulated necrosis carried out by the activation of RIPKs (receptor-interacting kinases) and MLKL (mixed lineage kinase–like). Active MLKL damages the plasma membrane of cells, results in PS exposure, and kills the cell by lysis. However, provided that MLKL activity is halted, cells can survive in a process termed resuscitation by ESCRT-mediated membrane repair.

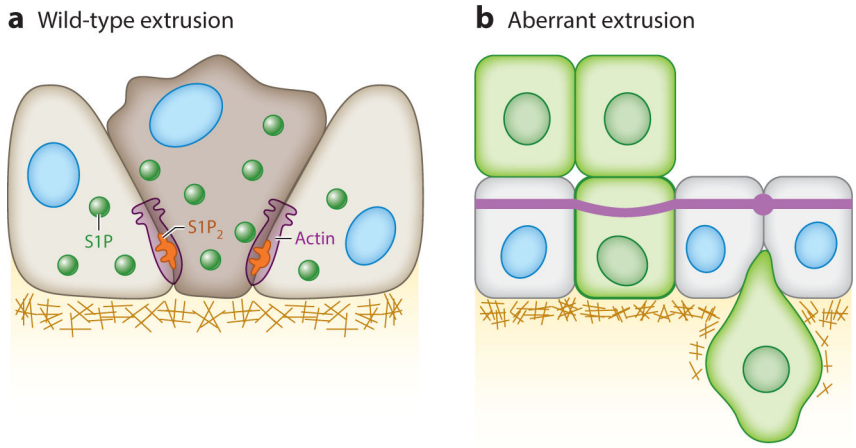

Figure 2.

Extrusion removes epithelial cells in response to crowding forces during homeostasis or apoptotic stimuli. (*a*) During apoptotic apical extrusion, the cell destined to die produces the bioactive lipid sphingosine-1-phosphate (S1P), which binds to the sphingosine-1-phosphate 2 ($S1P_2$) receptor in the neighboring cells to activate actomyosin contraction and squeeze the extruding cell out. These cells then die by anoikis or death due to loss of matrix-dependent survival signaling. (*b*) Disruption of apical extrusion signaling in epithelial cells (*green; normal cells are shown in gray*) can lead to formation of masses at sites where cells should have extruded and died and to basal extrusion, which enables invasion and initiation of metastasis. Oncogenic mutations in K-Ras and APC, and downregulation of $S1P_2$, disrupt apical extrusion and may account for the chemoresistance and highly invasive nature of pancreatic, lung, and colon tumors driven by these mutations.

Table 1

Major cell death modalities with biochemical hallmarks

Cell death pathway	Biochemical hallmarks	Reference(s)
Apoptosis	Caspase3/7 activation, PS exposure	Martin & Green 1995, Martin et al. 1995, Taylor et al. 2008
Autophagic cell death and autosis	Dependency on autophagy machinery	Bursch 2001, Liu et al. 2013
Necrosis	Plasma membrane lysis	Vanlangenakker et al. 2012
Secondary necrosis	Caspase-3-dependent cleavage of DFNA5	Rogers et al. 2017
Pyroptosis	Inflammatory caspase activation	Cookson & Brennan 2001, Man et al. 2017
Necroptosis	RIPK activation, MLKL activation	Ashkenazi & Salvesen 2014, Cho et al. 2009, Sun et al. 2012
Ferroptosis	Glutathione peroxidase inactivation, iron-dependent ROS accumulation	Dixon et al. 2012, Yang et al. 2014
Phagoptosis	Exposure of eat-me signals, loss of don’t-eat-me signals	Brown & Neher 2012
Entosis	Rho and ROCK activity, actomyosin contractions	Overholtzer et al. 2007
Cornification	Caspase-14 activation	Eckhart et al. 2013
Parthanatos	PARP-1 overactivation	Fuchslocher Chico et al. 2017
Linker cell-type death	HSF-1 induction of LET-70/UBE2D2	Malin et al. 2016
NETtosis	NADPH oxidase activity, formation of NETs	Remijsen et al. 2011

Table 2

Major cell survival pathways

Survival pathway	Biochemical hallmarks	Reference(s)
Anastasis	Survival after caspase-3/7 activation	Ding & Sun et al. 2016, Sun et al. 2017, Tang et al. 2012
Necroptosis resuscitation	Survival after MLKL activation	Gong et al. 2017a,b; Zargarian et al. 2017
Overriding anoikis	EGFR upregulation, PI3K/AKT activation	Frisch et al. 2013, Hanahan & Weinberg 2011, Kim et al. 2012
Hijacking entosis	E-cadherin overexpression, glucose starvation	Sun et al. 2014
Basal extrusion	Mutations in K-Ras, APC, and $S1PR_2$; disruption in SIP trafficking	Slattum et al. 2014