Cell Death versus Cell Communication

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Although every type of cell death proceeds through different stages, it is when it has reached the point of no return, where the decay inflicted to it is irreversible, that a cell would be considered dead. However, determining the point of irreversible decay is not an easy task. Cell–cell communication can be realized by many different modes. In addition to secreted chemicals such as growth factors, cells can interact via direct contact between their cytoplasmic membranes. All these modes have been implicated, in one way or another, either in responding to or conveying cell death signals.

apoptosis autophagy ferroptosis pyroptosis intercellular communication

1. Extruding the Dead

The intestinal epithelium is among the most rapidly renewing tissues in the body. Stem cells are responsible for replenishing the epithelium in cells, as their division generates precursor cells which proliferate and differentiate, while moving away from the crypt base towards the villus tip, from where they are later shed into the lumen [1][2]. This migratory process, therefore, determines the intestinal epithelial cells' (IECs) lifespan, and any abnormalities could have serious implications, whether in chronic inflammation-associated diseases or in tumorigenesis [3]. It has been suggested that, in the confinement of the villus tip, the high cellular density resulting from continuous proliferation induces cell death and shedding [4]. This homeostatic process is complex and involves multiple players [5][6]. Dying cells communicate with their neighbors, after which the latter undergo actin/myosin contraction to extrude out the dying cell [7]. The epithelium's barrier function, measured by electrical resistance, is maintained during the extrusion process and so are the plasma membrane integrity, AJs, and TJs [4]. These junctions are indeed essential for maintaining the intestinal epithelial barrier during IEC shedding [8].

TJs and AJs are adhesive molecular complexes involved in intercellular communication and in the maintenance of normal cellular integrity and cell–cell barriers. TJs are essential for cell polarity in epithelial cells and paracellular permeability in endothelial tissues [9]. Loss of TJ is incriminated in many aspects of tumor progression, including polarity, differentiation, adhesion, migration, invasion, and metastasis [10][11][12][13]. TJs bind to the cytoskeleton and have an intracellular signaling function [9], mediated by an interaction with cytoplasmic adaptor proteins (e.g., zonula occludens, i.e., ZO) or transmembrane linker proteins (e.g., occludin, claudins, and junctional adhesion molecules, i.e., JAMs) [12][14][15][16][17][18][19]. AJs are also important for epithelial tissues and use cadherins and related proteins to connect cytoskeletal structures between cells. Through their cytoplasmic domains, cadherins associate with actin filaments-based cytoskeletal structures [20][21]. AJs link the actin filaments of interacting cells at sites of cell–cell adhesion [22]. TJ rearrangement is important for the process of extrusion of dying cells from the

epithelium and barrier maintenance [23]. Although not formally addressed, the fact that IECs' death involves both a cytoskeletal reorganization and the maintenance of junctional integrity and function directly implicates these junctions in the process of cell death sensing and extrusion of the dying cell [4][7]. Interestingly, the latter communicates out its signal to request extrusion early in the apoptotic process, even before caspase activation and the appearance of apoptotic morphological changes or phagocytosis [7]. If anything, TJs and AJs could ensure the closing off of the intercellular gap left by the extruded cell and maintain confluence within the epithelial barrier [24].

In few words, dying cells take care of their own funerals. In the case of gut homeostasis, this is elegantly accomplished via soliciting the cytoskeletal connection with cell–cell junctions, to extrude them, while leaving behind a preserved epithelial barrier integrity.

2. Setting Fire

One cannot talk about intestinal epithelium homeostasis without talking about inflammation. In fact, the gastrointestinal tract is a place where cell death, intercellular communication, and inflammation are intimately linked.

The biggest threat to the integrity of the modes of cell–cell communication does not come from within the epithelium. Enteric bacterial pathogens have tremendous effects on junction barriers tasked with keeping them at bay. They try to alter these junctions in order to increase epithelial permeability and, whenever possible, to cross the barrier altogether [25]. In turn, epithelial cell turnover can be increased as a mechanism of expelling pathogens [26]. Such interactions between pathogens and the intestinal epithelium are under the control of an inflammatory process that, when interrupted, could lead to higher levels of apoptosis of IECs, the impaired production of antimicrobial peptides, and, ultimately, the invasion of the mucosa by pathogens [27].

Inflammatory cytokines released by immune cells constitute a threat to the intestinal barrier's integrity, particularly in conditions such as those found in inflammatory bowel disease [28]. However, this effect of inflammation on increased permeability, in many instances, does not involve apoptosis [29]. In fact, as has been seen above, apoptotic cells signal to their neighbors to extrude them and rearrange TJs to close the gaps [7][8].

Cell death of IECs has been reported to occur not only via apoptosis but also through inflammation-regulated necrosis, necroptosis, and pyroptosis [30]. Excessive apoptosis has been associated with inflammation in the intestine [31]. While this can result from a pathological condition, inflammation in IECs is also part of a mechanism of host protection against potentially harmful enteric pathogens. Another mechanism through which apoptosis could promote inflammation and immunity is by releasing EVs [32][33]. Many mechanisms are at play. For instance, EVs can participate in antigen presentation [33][34]. In addition, extruded apoptotic cells release ABs that, upon engulfment, stimulate cytokine production by the phagocyting cell [35]. Necroptosis has also been involved in intestinal inflammation and tumorigenesis [36][37]. Pyroptosis is also an important part of the host defense arsenal in epithelial tissues [38]. Activation of the inflammasome has been involved in IEC extrusion, along with a loss of plasma membrane integrity and death by pyroptosis. Here, again, the expulsion process is associated with major

actin rearrangement in neighboring cells, tasked with maintaining the intestinal epithelium's integrity [39]. Gasdermins (GSDMs), the principal effectors of pyroptosis [40][41][42][43] which also regulate mitochondrial oxidative stress [44] and are involved in the regulation of autophagy [45][46], have been assigned multiple functions in gut inflammation [47]. While autophagy is important for intestinal epithelium homeostasis [48] and, in fact, for the host's defense against pathogens [49], it counteracts inflammation [50][51], a function which is important in inflammatory pathogenesis such as in inflammatory bowel diseases [52].

In conclusion, the regulation of the epithelial barrier's integrity, performed by TJs and AJs, involves a mechanism of extrusion of the dying cells. Pathogens constitute a threat to this process, and it is only normal that, in the response of the host gut to this challenge, inflammatory processes dominate. Therefore, the recourse of the intestinal epithelium to pyroptosis and other inflammation-dependent forms of cell death makes the most sense, even if this entails a risk of perturbing cell–cell interactions and damaging the epithelial barrier's integrity.

3. Trying to Fit In

In the intestine, two systems of intercellular communication work in concert to accompany the course of cell renewal, migration, and differentiation. While TJs and AJs are important for the integrity of the epithelial layer, the Wnt/β-catenin/Tcf pathway regulates cell positioning in the crypt in addition to coordinating intestinal stem cells' migration and proliferation, via Ephs and ephrins [53][54]. And, while the junctional mode has a critical impact on inflammatory diseases, research has proven a tremendous impact of Ephs/ephrins on tumorigenesis.

Ephs/ephrins constitute, in fact, the largest subfamily of receptor tyrosine kinases (RTKs), a fact which fueled interest in using them as targets in cancer therapy [55][56][57]. Ephs and ephrins were initially described as guidance molecules, although it is their discovery in cancer cells which gave them their name (Erythropoietin-producing human hepatocellular carcinoma). This is a large family that enlists both receptors and their ligands called ephrins. In mammals, there are fourteen Eph receptors interacting with eight Ephrin ligands. Both Eph receptors and ephrin ligands are membrane-bound, thus eliciting a bidirectional signaling in the interacting pair of cells [58]. They constitute an intercellular communication mode with many functions, such as the formation of spatial boundaries during normal development [59][60][61][62][63][64][65][66][67][68][69][70][71][72][73][74][75][76]. While they regulate processes such as proliferation, cell death, and invasion, it is their role in cell sorting and positioning that made their fame [77][78], for instance, in regulating the positioning of intestinal epithelial cells within the stem cell niche [54] and coordinating between intercellular communication, migration, and cell positioning [53].

EphB2 and EphB3, two members of the Eph/ephrin family, are major elements of the genetic module that controls the compartmentalization of epithelial cells along the crypt axis and are involved in the regulation of their ordered migration [53].

In recent years, a role for Ephs and Ephrins deregulations has emerged in cancer progression and metastasis [79][80][81]. The EphB2 receptor has been reported as a tumor suppressor in the colon [82]. The initial observation was that EphBs are transcriptionally regulated by the β-catenin/Tcf signaling pathway, a major player in human

colorectal cancer progression [83][84]. While cells in early lesions of dysplastic crypts and small adenomas, like normal crypt progenitor cells, were found to express EphB2, high-grade tumor areas contained EphB2-negative cells [82][83][84]. Therefore, colon cancer progression is associated with a loss of EphB2 expression. This was further confirmed in the $Apc^{Min/+}$ mouse model of hereditary colon cancer and in many sporadic cancers [85]. Colorectal neoplasms in the $Apc^{Min/+}$ mice usually fail to cross the adenoma-carcinoma transition. Crossing $Apc^{Min/+}$ mice with animals expressing a dominant negative form of EphB2 resulted in a loss of EphB activity that accelerated colorectal tumor progression. In addition, high levels of EphB2 expression were found to be associated with a longer mean duration of survival in colorectal cancer [86], and a loss of EphB2 expression has been reported in colorectal tumors [87][88]. These findings support a tumor suppressor function of EphB2.

Tumor suppression can be achieved by inhibiting cell proliferation or inducing cell death or differentiation. Many Eph/ephrin family members have functions in cell death [89]. EphB2 has been found to regulate the proliferation of intestinal stem cells [54]. Furthermore, EphBs' role in tumor suppression is performed by limiting the expansion of colorectal cancer cells to specific compartments, rendering difficult the incursion of EphB-expressing cells into areas of high repulsive forces from normal ephrinB-expressing intestinal cells [83]. In fact, a decreasing gradient of EphB2 expression, from the bottom to the top, is found in the proliferative crypt of the small intestine. In the large intestine, EphB2 is expressed only in the progenitor cells at the crypt base. By contrast, the EphB ligands EphrinsB1 and B2 are expressed, also as a gradient, by the differentiated surface and villus cells [83]. During tumorigenesis, the loss of EphB receptors relieves cells from spatial restriction and allows cells to intermingle freely and invade [90]. The tumor suppression effect of EphBs, by controlling the compartmentalization of tumor cells, depends on E-cadherin-mediated adhesion [90]. EphB/ephrinB interaction has also been shown to promote mesenchymal–epithelial transition (MET), reorganizing the cytoskeleton and restoring epithelial E-cadherin/ZO-1-based cell–cell junctions [91]. These effects were also accompanied by the induction of apoptosis [91].

Autophagy is important in intestinal biology through controlling the TJs barrier function, as a survival mechanism, and by regulating intestinal stem cells' metabolism [92]. Although the data on the function of Ephs/ephrins in autophagy are scarce, the available information supports a direct connection. Researchers have previously shown that EphB2 regulates an autophagy-dependent cell death [93][94]. EphB/ephrinB interaction was shown to use autophagy to clear IECs of intracellular pathogens [95]. Silencing of EphA1 and EphB2 was shown to block autophagy and cell death in colorectal cancer cells [96]. Further investigation is needed.

And now, a few words about the function of Ephs and ephrins in inflammation and immunity that has increasingly been acknowledged [97][98]. The role of these proteins in angiogenesis is one of the first and most studied aspects of their biological functions [99]. A major part of the function of Ephs/ephrins in gut inflammation involves synaptic plasticity and the neuroimmune regulation of intestinal inflammation-related pathogenesis [97]. The relevance of the functions of Ephs/ephrins in inflammation and immunity in colorectal cancer remains, however, to be further examined. A possibility is via a role in the tumor's immune microenvironment [56][100]. However, how cell death could be involved is an important question deserving of attention in view of the above-discussed association between inflammation and cell death.

4. Surviving Attacks

Since intercellular communication is functionally connected to cell death, it is no surprise that it plays a role in cancer therapeutic resistance. However, the extent to which the balance between the two processes, i.e., communication and death, is important for drug resistance, could be easily identified as an area of unmet need in cancer research.

Data regarding the role of Ephs and ephrins in colon cancer drug resistance is still sporadic. EphB2 was found as one of the genes whose expression is increased in colon cancer cells resistant to platinum or taxane [101]. Acquisition of resistance to cetuximab, an antibody-based EGFR inhibitor, is associated with an increase in EphB3 expression levels and EphB3/EGFR binding in colorectal cancer cells. The mechanism of resistance can be overcome by inhibiting EphB3 expression, which allows cetuximab-induced apoptosis [102]. Claudin-1 (CLDN1) promotes colorectal cancer (CRC) cells' chemoresistance by interacting with and stabilizing EphA2. This results in enhancing the antiapoptotic AKT signaling pathway and promoting cancer stemness [103]. Directly targeting EphA2 with a tyrosine kinase inhibitor decreases cell proliferation and induces cell death in CRC cells [104][105][106]. Based on the finding that, in response to DNA damage, the ephrinB2-encoding gene is a transcriptional target of p53, a key apoptosis regulatory protein, knock down of ephrinB2 expression was used to restore apoptosis and 5-FU chemosensitivity in mutant p53-harboring CRC tumors [107]. The physical and functional association between EphA2 and EGFR plays a role in the resistance to EGFR-targeting therapies [108]. High EphA2 expression levels are associated with a worse outcome in patients treated with cetuximab [109]. Metastatic CRC cells that have NRAS (neuroblastoma RAS viral oncogene homolog)-activating mutations are resistant to cetuximab. A failure of cetuximab to downregulate EphA2 expression in NRAS-mutant CRC cells, in comparison with cetuximab-responsive CRC cells, was suggested as a potential contributor to resistance to this drug [110]. The use of the ephrinA1 ligand to activate EphA2 succeeds in restoring cetuximab activity in NRAS-mutant colorectal cells [110]. Although it is not clear whether the mechanism involves an effect on apoptosis or another type of cell death, it was shown to involve the suppression of mitogen-activated protein kinase (MAPK) and AKT hyperactivation. The roles of these pathways in both apoptosis and Ephs/ephrins signaling are established [111]. An EphA2 small-molecule inhibitor could be used successfully to reverse cetuximab resistance in CRC cells by inducing apoptosis and cell cycle G1–G2 arrest and inhibiting the MAPK and AKT pathways [112]. Although shown in a different type of cancers, i.e., head and neck squamous cell carcinoma, resistance to cetuximab and radiotherapy (RT) was associated with elevated EphB4 and ephrinB2 expression levels [113]. The therapeutic response to cetuximab-RT could be improved by concomitantly blocking the EphB4–ephrinB2 interaction that results in the inactivation of the AKT and MAPK pathways, a decrease in proliferation, and an increase in apoptosis [113]. Similarly, in non-small-cell lung cancers, silencing of ephrinB3 sensitizes cells to a combined treatment with the kinase inhibitor PKC 412 and ionizing radiation [114]. Here, again, the MAPKs and Akt signaling pathway are involved, which elicit a decreased proliferation, increased apoptosis, mitotic catastrophe, and senescence signaling [114]. These data point to a prominent role for the MAPK and AKT pathways and apoptosis. However, the link with Eph/ephrin-mediated intercellular communication awaits further direct investigation. Interestingly, MAPK inhibition along with tyrosine phosphorylation of cell junction proteins such as CLDN1 was observed in cetuximab-responsive tumors compared to their resistant counterparts [115].

While apoptosis' prominent role in mechanisms of CRC drug resistance is well documented [116][117][118], data are in favor of an equally critical function for autophagy and autophagy-dependent cell death [119][120]. A balance between apoptosis and autophagy, controlled by p38MAPK, has an important role in resistance to 5-FU [121]. Autophagy is involved in the resistance of CRC cells to EGFR targeting using a monoclonal antibody [122]. In this case, autophagy acts as an adaptive survival mechanism because, when inhibited, the response to the drug by increasing cell death is improved using an autophagy inhibitor [122]. In fact, a combined targeting of both EGFR and autophagy is a tempting yet still underexplored strategy to bypass drug resistance in CRC [123]. To date, only a handful of publications have addressed the regulation of autophagy by Ephs and ephrins in cancer, including in CRC cells [93][94][95][104][124]. Whether this function could impact therapeutic drug responsiveness is unknown. There are even less data regarding other modes of cell death, especially ferroptosis or pyroptosis. Ferroptosis is increasingly viewed as a possible therapeutic target in CRC [125][126]. When other modes of cell death such as apoptosis fail, the induction of ferroptosis succeeds in eliminating CRC cells [127]. This is understandable, knowing that inhibition of ferroptosis by iron sequestration results in CRC progression and resistance to 5-FU [128].

In addition to Ephs and ephrins, the role of connexins in drug resistance has also been recognized, although it is sometimes paradoxical depending on whether they act via GJIC or not. Expression of some connexins has been associated with chemoresistance in a GJIC-independent manner [129][130][131]. However, GJIC can also directly contribute to these mechanisms, as in the case of fibroblasts which protect lung tumor cells from death by connecting with them via GJICs, thus resulting in cancer cells' chemoresistance [132]. The BE mediated by GJIC increases cisplatin cytotoxicity, and the inhibition of Cx43 expression results in drug resistance [133]. In fact, the induction of connexin expression and/or the activation of GJIC have long been viewed as strategies to overcome chemoresistance or, as will be seen below, to improve the response to gene or radiation therapies. In CRC, 5-Fluorouracil (5-FU) is one of the most important chemotherapeutic drugs in use. However, resistance emerges to this drug [134]. A correlation exists between a loss of CX43 expression, metastasis, and poor prognosis, while restoring Cx43 expression leads to the suppression of CRC progression and an increase in the sensitivity to 5-fluorouracil (5-FU) [135]. In addition to 5-FU, the resistance of CRC cells to oxaliplatin and irinotecan is also associated with a loss of Cx43 expression [136]. The use of resveratrol, a natural polyphenol, has been explored to chemosensitize CRC cells to 5-FU. The mechanism involves the upregulation of cell–cell communication molecules that constitute desmosomes, gap and tight junctions, and adhesion molecules, while also enhancing the onset of apoptosis [137]. Similarly, one of the mechanisms through which all-trans retinoic acid (ATRA) is able to restore the resistance of CRC cells to paclitaxel is by improving Cx43-dependent GJIC [138]. However, this effect relies more on a role for Cx43 in reducing CRC cells' migration and invasiveness rather than inducing apoptosis [138]. The connection between these functions of connexins and GJIC in drug resistance with various types of cell death has not been addressed specifically. Some data from other types of cancer could provide some insight. For instance, while Cx43 was reported to have a role in resistance of glioblastoma (GBM) cells to temozolomide (TMZ) thanks to an anti-apoptotic effect [131], when combined with a Cx43 inhibitor, responsiveness to TMZ is improved by inhibiting AKT signaling and inducing both autophagy and apoptosis [139]. Furthermore, under regulation by EGFR/MAPK signaling, Cx43 expression is increased in TMZ-resistant GBM cells [140]. Knocking down Cx43 expression sensitizes GBM cell to TMZ [140]. Perhaps, more spectacularly, through establishing GJIC with

neighboring astrocytes, GBM cells can resist TMZ-induced apoptosis, an effect which is prevented by the knockdown of astrocytic Cx43 expression [141]. These and other data put forward the potential use of connexin and GJIC targeting as an approach to counteract TMZ resistance [142]. Connexins and autophagy have a reciprocal relation, each being both target and regulator of the other [143]. This is the case in cervical cancer cells where the overexpression of connexin32 (Cx32) promotes autophagy in a GJ-independent manner, subsequently inducing apoptosis [144]. Nevertheless, within this equation, Cx32 has another GJIC-independent function, as it suppressed apoptosis induced by combined treatment with an autophagy inhibitor and cisplatin [145]. This anti-apoptotic effect is mediated by the Cx32-driven upregulation of EGFR expression and could be abrogated using an EGFR inhibitor [145].

In summary, intercellular communication, whether via Eph/ephrin, EVs, GJs, TJs, or AJs, has essential functions in the homeostatic regeneration of the gut, its response to pathogens, its blockade of tumor progression, and its response to therapeutic agents. While some of these roles directly implicate apoptosis and, to a lesser extent, autophagy, some other roles rely more on a role as positioning, sorting, and guidance systems (Ephs and ephrins).

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