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Review

The role of necroptosis in cancer: A double-edged sword?

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ABSTRACT

Necroptosis is a programmed, caspase-independent cell death that is morphologically similar to necrosis. Unlike apoptosis, necroptosis evokes inflammatory responses by releasing damage-associated molecular patterns. Recent studies suggest that tumor undergoes necroptosis *in vivo* and necroptosis has pro- or anti-tumoral effects in cancer development and progression. Furthermore, triggering necroptosis in tumor cells has been explored as a potential therapeutic strategy against cancer. Here, we will review the recent research progress of necroptosis in conferring anti- or pro-tumoral effects and its potential application in cancer therapy.

1. Introduction

Programmed cell death (PCD) is a genetically regulated process leading to the death of cells. It is indispensable for biological process of mammals such as organismal development, physiological homeostasis, epithelial cell renewal and lymphocyte selection [1]. Apoptosis is a caspase-dependent cell death and had been considering as the only form of PCD for a long time. Contrary to apoptosis, necrosis was previously believed to be an accidental form of cell death that occurs upon cellular insults because of physical stresses. However, this conception has changed recently with the discovery of other types of PCDs with necrotic morphology including necroptosis, pyroptosis, ferroptosis, pyronecrosis, parthanatos, oxytosis and NETosis [2]. Morphologically similar to necrosis, necroptosis is characterized by a gain in cell volume, swelling of organelles, plasma membrane rupture, and subsequent loss of intracellular contents [3–5]. Unlike apoptosis, necroptosis is a caspase-independent cell death. It is now known that the serine/threonine kinases, RIPK1 and RIPK3, and MLKL are essential for TNF-induced necrotic cell death [6–12]. Current studies suggest that necroptosis contributes to the pathophysiology of various inflammatory, infectious and degenerative diseases [11,13–15].

Tumor necrosis is commonly observed in core regions of solid tumor because of the metabolism stresses such as hypoxia and glucose deprivation (GD). This type of necrosis has been found to be associated with tumorigenesis and poor prognosis for years [16]. However, the role of necrosis in cancer development and progression is still largely unknown due to the lack of experimental system for manipulating necrotic cell death. As necroptosis is morphologically similar to necrosis, studies on the molecular mechanism of necroptosis have improved our understanding about the role of necrosis in tumorigenesis. For example, a recent study demonstrated that the key components of the necroptosis, RIPK1 and RIPK3, were highly expressed in pancreatic ductal adenocarcinoma (PDA), and inhibition of RIPK3-mediated necroptosis delayed PDA progression [17]. However, necroptosis also inhibits tumor progression by releasing damage-associated molecular patterns (DAMPs) to elicit robust cross-priming of anti-tumor CD8+ T cells [18]. Thus, necroptosis is involved in tumor necrosis, yet it is still not clear what role does necroptosis play in tumorigenesis. In this review, we will

Abbreviations: DAMPs, Damage-associated molecular patterns; PCD, Programmed cell death; RIPK1, Receptor-interacting protein 1; RIPK3, Receptor-interacting protein3; MLKL, Mixed lineage kinase domain-like protein; PDA, Pancreatic ductal adenocarcinoma; TLR3, Toll-like receptor 3; TNF-R1, TNF-receptor I; TRADD, Tumor necrosis factor receptor type 1-associated DEATH domain protein; TRAF2, TNF receptor-associated factor 2; cIAP, Cellular inhibitor of apoptosis; FADD, Fas-associated protein with death domain; CYLD, cylindromatosis; RHIMs, RIP homotypic interaction motifs; TICAM1, Toll like receptor adaptor molecule 1; DAI/ZBP1/DLM-1, DNA-dependent activator of interferon regulatory factors; IP, inositol phosphate; RARγ, Retinoic acid receptor gamma; CHIP, Hsp70-interacting protein; PELI1, Pellino E3 ubiquitin protein ligase 1; MK2, MAPKAP kinase-2; AML, Acute myeloid leukemia; CLL, Chronic lymphocytic leukemia; HCC, Hepatocellular carcinoma; MAPK, Mitogen-activated protein kinase; TME, Tumor microenvironment; DSS, Dextran sulfate sodium; EC, Endothelial cell; TC, Tumor cell; DR6, Death receptor 6; ICC, Intrahepatic cholangiocarcinoma; IL-1α, Interleukin-1α; DC, Dendritic cells; NKT, Natural killer T; 5-FU, 5-fluorouracil; IFN, Interferon; IRF, IFN-regulatory factor; ALL, Acute lymphoblastic leukemia; NHL, Non-Hodgkin lymphomas

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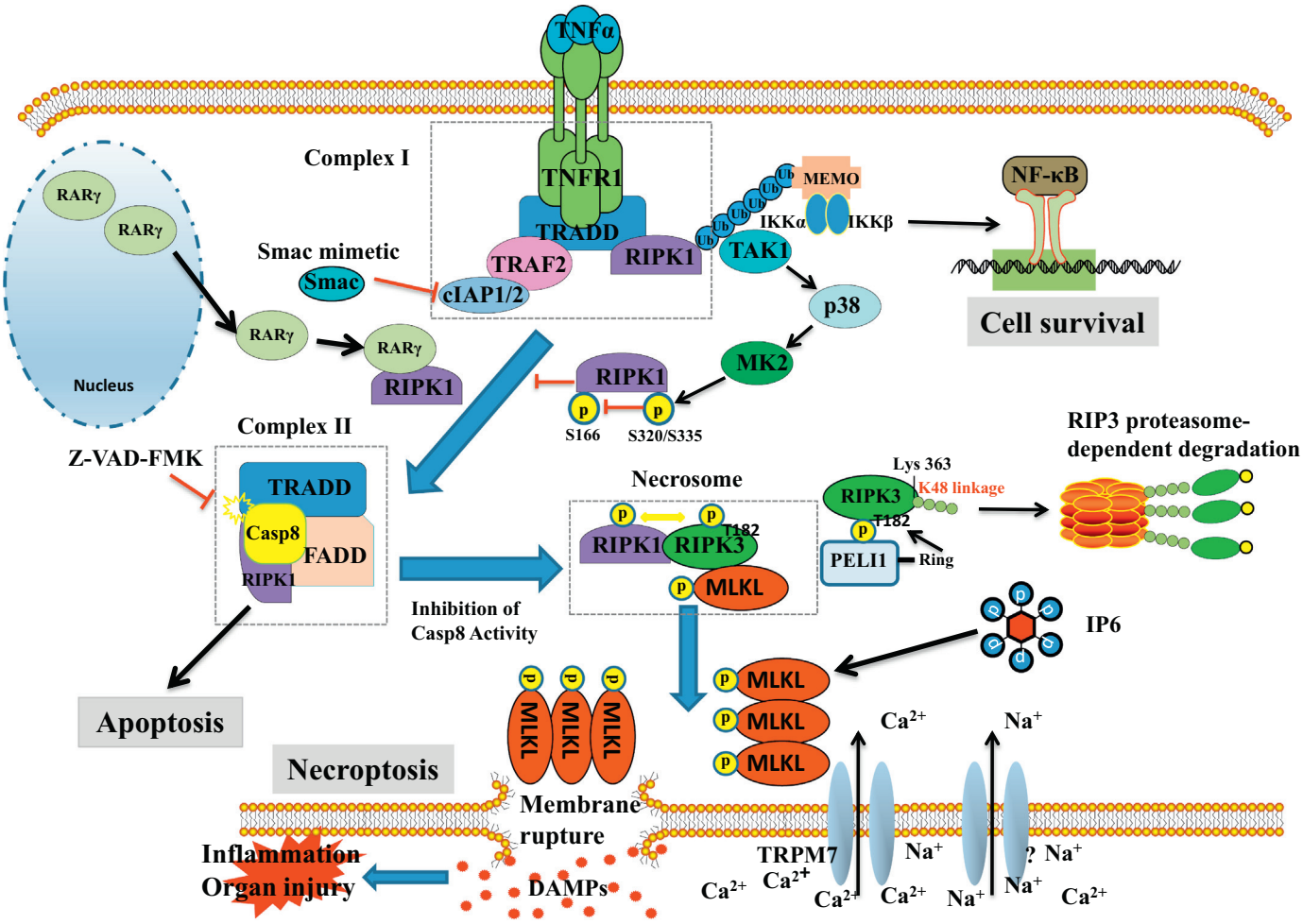

Fig. 1. Molecular mechanism of TNFα-initiated necroptosis.
Ligation of TNF-R1 results in the formation of membrane-signaling complex termed Complex I , which includes TRADD, RIPK1, TRAF2, and cIAP1/cIAP2. The complex I leads to the activation of NF-κB signaling pathway, which promotes cell survival and inflammation. The polyubiquitination of RIPK1 by cIAP1/cIAP2 is essential for the activation of NF-κB signaling pathway. When cIAPs are inhibited by Smac or smac mimetic compounds, RIPK1 is deubiquitinated. Then, the Complex I is released into the cytosol and recruits FADD to form Complex II. FADD is imperative for inducing the dimerization and activation of caspase-8, which executes the process of apoptosis. In this scenario, RARγ translocates from nucleus and interacts with RIPK1 to promote its dissociation from complex I. MK2 is an inhibitor for RIPK1-dependent PCD. MK2 is activated by p38/MAPK pathway and directly phosphorylates RIPK1 at residue S320/S335. This phosphorylation inhibits auto-phosphorylation of RIPK1 at residue S166 and thus prevents formation of Complex II. Inhibition of caspase-8 activity by zVAD-FMK allows recruitment of RIPK3 to the Complex II to form Necrosome. The formation of Necrosome switches the death signals from apoptotic to necrotic. PELI1 is a K48 ubiquitin ligase for phosphorylated RIPK3. It induces RIPK3 degradation through the proteasome pathway to inhibit necroptosis. Then, MLKL is recruited to the Necrosome and phosphorylated by RIPK3, leading to its oligomerization and plasma membrane localization. The oligomerization and plasma membrane translocation of MLKL are regulated by IPs, which bind to MLKL and displace its auto-inhibitory brace to inhibit activation of MLKL. The plasma membrane translocation of MLKL is essential for rupture of plasma membrane, either by directly forming pore structures or activating cation channels to increase Ca^{2+} and Na^{+} ion influx, which enhance cellular osmotic pressure and finally rupture the plasma membrane. When plasma membrane is ruptured, DAMPs in the cytosol are released, leading to tissue inflammation and organ injury.

summarize and discuss the potential roles of necroptosis in cancer and the relevance of necroptosis in anti-cancer therapy.

2. Molecular mechanisms of necroptosis

The initiation of necroptosis can be triggered by the engagement of death receptors in the TNF superfamily, TLR3 or TLR4 and the interferon receptors [19–23]. TNF-α induced necroptosis is the best characterized signaling pathway for necroptosis. Ligation of TNF-α homotrimer with TNF-R1 results in the formation of membrane-signaling complex termed complex I , which includes TRADD, RIPK1, TRAF2, and cIAP1/cIAP2. The complex I leads to the activation of pro-survival pathways involving NF-κB and MAP kinases [24,25]. In this scenario, polyubiquitination of RIPK1 by cIAP1/cIAP2 and LUBAC is essential for the activation of NF-κB signaling pathway [26] (Fig. 1).

When deubiquitination of RIPK1 is favored (for instance, inhibition of the IAP protein family by Smac or chemical compounds like Smac mimetics), the complex I is released into the cytosol and recruits FADD to form complex II [27]. FADD is imperative for inducing the dimerization and activation of caspases, which executes the process of apoptosis. Active caspase-8 not only initiates the apoptosis but also prevents necroptosis because it cleaves essential mediators of necroptosis such as RIPK1, RIPK3 and CYLD. Thus, inhibition of caspase-8 activity allows recruitment of RIPK3 to the complex II to form the necrosome [28–30]. In the necrosome, RIPK1 interacts with RIPK3 to form large amyloid-like complexes through the RIP homotypic interaction motifs (RHIMs) [11,12,31]. The recruitment of RIPK3 into the complex II switches the death signals from apoptotic to necrotic. Then, MLKL, a downstream substrate of RIPK3 kinase, is recruited to the necrosome by interacting with RIPK3. Phosphorylation of MLKL by

Table 1
Expression of necroptosis core proteins in cancer and their impacts on cancer prognosis.

	Expression level	Tumor type	Prognosis	Ref (s)
RIPK1	High protein level	Glioblastoma, melanoma, lung cancer, PDA, and HCC	Poor prognosis in glioblastoma and HCC	[17,67–70]
RIPK3	High protein level	PDA	ND	[17]
	Low protein level	AML, CLL, ovarian cancer, breast cancer, and colorectal cancer	Poor survival in ovarian cancer, breast cancer, and colorectal cancer	[52,55–60]
MLKL	High protein level	Both human and mouse breast cancer, cervical squamous cancer	Improved overall survival for cervical squamous cancer	[61,65]
	Low protein level	Ovarian cancer and colorectal cancer	Poor prognosis in ovarian cancer and colorectal cancer	[63,64]
Phospho-MLKL	High protein level	Colon and esophageal cancer	Low overall survival in colon and esophageal cancer	[59,66]

ND: not determined; PDA: Pancreatic ductal adenocarcinoma; HCC: hepatocellular carcinoma; AML: Acute myeloid leukemia; CLL: chronic lymphocytic leukemia.

RIPK3 leads to oligomerization and plasma membrane localization of MLKL [32–35].The plasma membrane translocation of MLKL is essential for rupture of plasma membrane although the precise mechanism by which MLKL induces membrane rupture is not clear. Some reports implicated that calcium or sodium cation channels were activated and the ions flowed into the cytosol, which enhanced cellular osmotic pressure and finally ruptured the plasma membrane [33–35].Others showed that MLKL could form pore structures and directly breakdown the plasma membrane [32,34].When plasma membrane is ruptured, DAMPs in the cytosol are released, leading to tissue inflammation and organ injury [36] (Fig. 1).

RIPK1 is not the sole partner for RIPK3 to mediate necroptosis. At least two other RHIM-domain containing proteins can physically interact with RIPK3 to initiate necroptosis. One is the TICAM1 or TRIF, which functions as an adaptor in TLR3 and TLR4 signaling pathway to mediate TLR-induced necroptosis [19,21]. Another one is the DAI/ZBP1/DLM-1, which responds to exogenous DNA and interacts with RIPK3 to mediate virus-induced necroptosis [37]. So far, it is believed that RIPK3 and MLKL are the essential and indispensable components of necroptosis.

Recently, several molecules have been reported as critical mediators in necroptosis signaling pathway. Dovey et al. showed that IP kinases, which were encoded by IPMK and ITPK1, were required for necroptosis. In human cells, highly phosphorylated IPs bound to MLKL and potentially displaced the auto-inhibitory brace of MLKL to promote the oligomerization and plasma membrane recruitment of MLKL [38]. Another novel checkpoint in regulating necroptotic pathways is the cytoplasmic nuclear receptor RARγ. Xu et al. found that RARγ translocated from nucleus to cytosol in TNF-α-induced necroptosis and promoted RIPK1 dissociation from TNF-R1 complex (Complex I) to form cytosolic death signaling complex II [39].

Furthermore, the ubiquitination and phosphorylation of RIPK1 or RIPK3 provide early check points in TNF-α-induced PCD. It has been shown that the ubiquitination of RIPK3 targeting for degradation protected cells from necroptosis. For example, the carboxyl terminus of Hsp70-interacting protein (CHIP) and Pellino E3 Ubiquitin Protein Ligase 1 (PELI1) were identified as E3-ubiquitin ligases of RIPK3 to inhibit necroptosis by targeting RIPK3 for destruction [40,41]. On the other hand, the ubiquitination of RIPK1 or RIPK3 that are not associated with proteasomal degradation often promotes necroptosis. For example, K63 ubiquitination of RIPK1 has been shown to promote necroptosis, which was regulated by deubiquitylation enzyme A20 and the ubiquitin-binding protein ABIN-1 [42,43].It has been shown that the ubiquitination of the RIPK3 at Lys5 (K5) supported necrosome formation and necroptosis, which was negatively regulated by deubiquitylation enzyme A20 [42]. Intriguingly, although PELI1 has been shown to inhibit necroptosis by targeting RIPK3 for degradation [41], it was reported to promote necroptosis by inducing K63 ubiquitination of RIPK1 in another study [44]. The reason for discrepancy of these two studies is unclear and further studies need to be conducted to clarify the role of PELI1 in necroptosis. Phosphorylation of RIPK1 also plays an important role in regulating RIPK1-dependent apoptosis and necroptosis. RIPK1 can be phosphorylated by IKK1/2 [45], TAK1 [46], and its downstream effector mitogen-activated protein kinase (MAPK)-activated protein kinase (MK2) [47–49], as well as recently identified TANK-binding kinase (TBK)1 and IKKε [50,51]. The phosphorylation of RIPK1 by these kinases has been shown to prevent TNF-α-induced PCD.

3. Expression of necroptosis core proteins in cancer

As an essential component executing necroptosis, RIPK3 expression is often silent in a wide variety of cancer cell lines. It has been reported that hypermethylation of RIPK3 promoter contributed to the loss of RIPK3 expression and necroptotic resistance in cancer cell lines [52]. In this scenario, UHRF1,an epigenetic regulator, inhibited RIPK3 expression by maintaining the methylation status of RIPK3 promoter, while the transcriptional factor Sp1 positively regulated RIPK3 expression in RIPK3-expressed cancer cells [53]. The loss of RIPK3 expression seems occur progressively during tumor growth and may be an oncogene-driven process. Two oncogenes, BRAF and AXL, were found as crucial factors among the driving forces for the loss of RIPK3 in cancer cells [54]. Consistently, reduced expression of RIPK3 was also found in human samples of several types of cancer including human AML, CLL, breast and colorectal cancers [52,55–59]. Low RIPK3 expression has been shown to be related to poor survival rates in ovarian, breast, and colorectal cancers [52,59,60]. However, in some subtypes of cancer, RIPK3 expression is found to be elevated. For example, analysis of TCGA database showed that RIPK3 expression was enriched in serous ovarian cancer [60]. In human PDA, RIPK1, RIPK3 and MLKL were highly expressed and the chemotherapy drug gemcitabine up-regulated the expression of RIPK1 and RIPK3 [17]. Furthermore, it has been recently demonstrated that RIPK3 and MLKL expression was significantly increased in the later stage of MMTV-PyMT mouse model of breast cancer [61]. Thus, RIPK3 expression seems varied among the tissue samples from different subtypes and stages of cancer (Table 1). In future, it would be important to investigate the temporal and spatial expression patterns of RIPK3 in different cancer subtypes.

Unlike RIPK3, MLKL is detected in multiple cancer cell lines and several subtypes of cancer. Low MLKL expression was associated with poor prognosis for gastric, ovarian and colon cancers [62–64].While high MLKL expression was related to improved overall survival for cervical squamous cancer [65] (Table 1).This suggests that escape from MLKL-mediated necroptosis might be a mechanism for tumor development and progression. However, high level of phosphor-MLKL has been shown to correlate with poor prognosis for colon and esophageal cancer patients [59,66] (Table 1).One possibility is that a subset of cancer cells undergoing necroptosis may modulate tumor inflammatory microenvironment to promote tumor progression. For example, it has been recently shown that phosphor-MLKL expression was increased during the progression of mouse model of breast cancer. When blocking MLKL-mediated necroptosis, both lung metastasis and the production of inflammatory cytokines were dramatically reduced, implicating necroptosis-induced inflammation might contribute to tumor metastasis [61].

As an essential component of TNF-α-induced necroptosis, RIPK1 expresses in most of cancer cell lines. High RIPK1 expression was reported in glioblastoma, melanoma, lung cancer, PDA, and HCC [17,67–70]. In addition, high RIPK1 expression was related to poor prognosis in glioblastoma and HCC [67,70] (Table 1). Since RIPK1 also mediates both TNF-α-induced NF-κB activation and apoptosis [71], carefully dissecting the necroptotic *versus* non-necroptotic functions of RIPK1 during tumor progression will be critical for clarifying the roles of RIPK1-mediated necroptosis in cancer.

4. Role of necroptosis in tumorigenesis and metastasis

Necroptosis is considered as an inflammatory mode of cell death due to release of intracellular DAMPs that promote inflammation. With DAMPs-induced inflammation, some signaling pathways, such as NF-κB or MAPK pathways, are activated, with many studies demonstrate that their activation has pro-tumoral effects [72].On the other hand, the release of DAMPs from necroptotic cells also promote maturation of dendritic cells and the cross-priming of $CD8^+$ T cells in TME, which in turn induce anti-tumor immunity [18,73–75].Thus, necroptosis plays a double-edged sword role by having both anti- and pro-tumoral effects during tumor progression (Table 2). Accumulating evidence imply that the pro- or anti-tumoral effects of necroptosis are likely dependent on the type, stage and grade of cancer. In this section, the effects of necroptosis on tumorigenesis and metastasis, as well as the influence on TME will be discussed.

4.1. The pro-tumoral effects of necroptosis

Necroptosis in tumor cells may modulate TME to promote tumorigenesis and metastasis. In PDA, RIPK1 and RIPK3 were highly expressed. *In vivo* deletion of RIPK3 or inhibition of RIPK1 delayed PDA progression in mice. This phenomenon was associated with enhanced anti-tumoral immune responses, as observed by increased infiltration of lymphocytes and decreased infiltration of immunosuppressive myeloid cells in RIPK3-deficient PDAs. As tumor cells undergoing necroptosis may release soluble factors favoring peri-tumoral immune suppression, two cytokines, CXCL1 and SAP130, were identified to be down-regulated in RIPK3-deficient PDAs. Conceptually, when RIPK3-mediated tumor necroptosis was occurred, the released soluble factors ligated with their receptors on inflammatory cells, such as SAP130 to its cognate receptor Mincle, to elicit an immune-suppressive tumor microenvironment (TME) and promote PDA progression [17] (Fig. 2). However, since RIPK3 also plays several other roles besides its necroptotic function [76], it is still not clear to what extent RIPK3-mediated necroptosis promotes the progression of PDA *in vivo*. Recently, Jiao et al. examined tumor necroptosis in a MMVT-PyMT mouse model of breast cancer by using an antibody specific for phosphorylated MLKL [61]. They found that necroptosis was ubiquitous in tumor necrotic areas and the phosphorylation level of MLKL was elevated in the later stage of breast cancer. Although both wild-type and MLKL deficient tumors grew at a similar rate, the lung metastasis was significantly inhibited by MLKL depletion, suggesting MLKL-mediated necroptosis in tumor cells promoted metastasis of breast cancer. As necroptosis is a pro-inflammatory cell death, the production of inflammatory cytokines was significantly reduced in macrophages from MLKL deficient tumors, indicating necroptosis induced inflammation may contribute to metastasis of breast cancer [61]. Collectively, these studies suggest that tumor necroptosis occurs *in vivo* and exhibits pro-tumoral effects by eliciting a pro-tumoral immune microenvironment.

The pro-tumoral effects of necroptosis are also driven by its execution on host non-tumoral cells. It has been reported that necroptosis in intestinal epithelial cells promoted carcinogenesis by inducing colonic inflammation. The E3 ubiquitin ligase HACE1 functions as a key regulator of TNF-R1-mediated signaling by directly mediating K63-linked ubiquitylation of TRAF2. Knockout of HACE1 in mice attenuated

Table 2
The pro- and anti-tumoral effects of necroptosis in cancer.

	Necroptotic cell type	Tumor type	Major findings	Ref (s)
Pro-tumoral effects	TCs	PDA	RIPK3-mediated necroptosis promotes immune suppressive TME by inducing the release of CXCL1 and SAP130	[17]
		Breast cancer	MLKL-mediated necroptosis promotes lung metastasis by inducing the production of inflammatory cytokines	[61]
	Intestinal epithelial cells	Colorectal cancer	Deficiency of HACE1 promotes RIPK3-mediated necroptosis, which leads to chronic colitis and colorectal carcinogenesis	[77]
	ECs	Breast cancer	DR6-mediated necroptosis in ECs promotes TC extravasation from EC layer and lung metastasis	[79]
	Hepatocytes	ICC	Necroptosis-dominated hepatic TME directs hepatocytes to ICC, which is epigenetically mediated by Tbx3 and Prdm5	[81]
Anti-tumoral effects	TCs	Cervical squamous cancer, colon cancer cell line CT26	TC necroptosis releases DAMPs (IL-1α, IL-12, etc.) to activate DCs and cross-priming of $CD8^+$ T cells	[18,73–75]

TCs: Tumor cells; ECs: Endothelial cells; ICC: Intrahepatic cholangiocarcinoma; DCs: dendritic cells; PDA: Pancreatic ductal adenocarcinoma; TME: Tumor microenvironment; DAMPs: Damage associated molecular patterns.

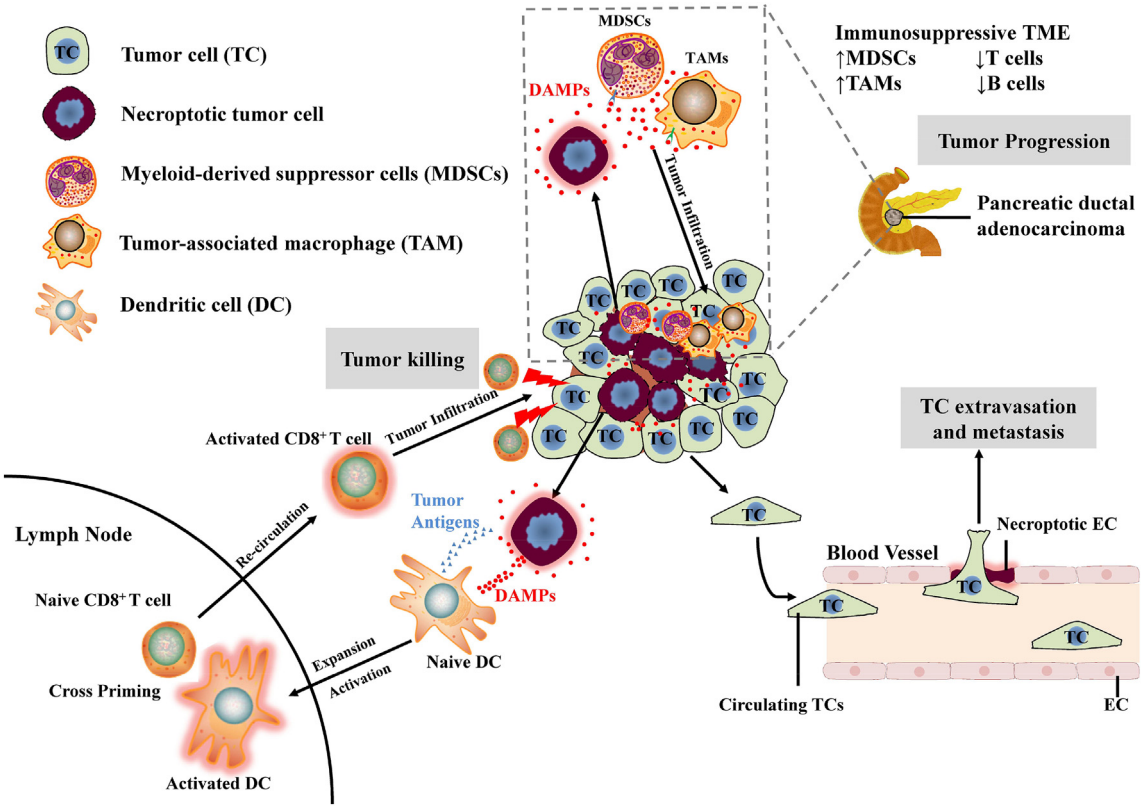

Fig. 2. The pro- and anti-tumoral effects of necroptosis in cancer.
In pancreatic ductal adenocarcinoma (PDA), DAMPs or cytokines released from necroptotic tumor cells recruit MDSCs and TAMs to induce an immunosuppressive TME. The immunosuppressive TME promotes tumor growth and progression. In addition, circulating tumor cells (TCs) induce necroptosis in endothelial cells (ECs) to enable TCs extravasation from necroptotic EC layer, which promotes tumor metastasis. One the other hand, the DAMPs released from necroptotic TCs also attract dendritic cells (DCs) to the tumor site and the activated DCs uptake tumor antigens to cross-prime naïve $CD8^+$ T cells in the lymph node. Then, the naïve $CD8^+$ T cells differentiate into cytotoxic T cells (CTLs) to infiltrate the tumor sites and kill tumor cells.

activation of NF-kB signaling and inhibited apoptosis, whereas TNF-R1-mediated necroptosis was not impaired. In this case, *in vivo* deletion of HACE1 in mice resulted in increased necroptosis of epithelial cells and damage of intestinal mucosal barrier, which consequently leaded to chronic colitis and colorectal carcinogenesis. Furthermore, genetic inactivation of RIPK3 or TNFR1 alleviates symptoms of colitis and carcinogenesis, suggesting RIPK3-mediated necroptosis promotes chronic inflammation and colorectal tumorigenesis [77]. In addition, applying pharmacological inhibitor for necroptosis in acute DSS-induced colitis, such as necrostatin-1, significantly suppressed colitis-associated tumorigenesis in mice [78].

In addition to intestinal epithelial cells, endothelial cell (EC) undergoing necroptosis might promote tumor metastasis by increasing tumor cell extravasation from EC layer (Fig. 2). Co-culture of tumor cells (TCs) with ECs leaded to DR6–mediated necroptosis in ECs and enhanced TC trans-endothelial migration. Knockdown of two mediators of necroptosis, RIPK3 or MLKL resulted in decreased EC necroptosis and TC migration over an EC layer. As expected, intravenous injection of metastatic TCs resulted in necroptosis of ECs and metastasis formation in wild-type mice, whereas endothelial cell-specific RIPK3 knockout mice and MLKL-deficient mice exhibited a reduction in necroptotic cells, TC extravasation, and metastases [79] (Fig. 2). However, one study suggested that although loss of RIPK3 in EC decreased transmigration ability of TC to cross the vascular endothelial layer, deletion of MLKL in mice had no effects on TC transmigration and lung metastasis. They further demonstrated that RIPK3 might function as a signaling platform to regulate permeability of EC layer in addition to its necroptotic function [80]. As these two studies were not based on the same tumor models, the exact role of EC necroptosis in modulating tumor metastasis may need to be confirmed in additional experimental models or additional cohorts of patients.

The inflammatory microenvironments induced by necroptosis not only favors tumor progression but also directs the lineage commitment during tumor development. One recent study demonstrated that with the activation of oncogenes, a necroptosis-dominated hepatic microenvironment induced hepatocytes to intrahepatic cholangiocarcinoma (ICC), while an apoptotic microenvironment induced hepatocytes to hepatocellular carcinoma (HCC). In this scenario, Tbx3 and Prdm5 were major microenvironment-dependent and epigenetically regulated lineage-commitment factors [81].

4.2. The anti-tumoral effects of necroptosis

The suppressive effects of necroptosis on tumor progression are initially suggested by clinical and histopathological studies. For example, low expression of necroptosis core proteins, RIPK3 and MLKL, were related to poor prognosis in colorectal cancer and ovarian cancer patients, respectively [59,63]. While up-regulated MLKL expression in cervical squamous cancer predicted a low histological grade, limited metastatic dissemination, and improved overall survival [65].

The anti-tumoral roles of necroptosis are further supported by experimental studies in tumor immunology. Necroptosis may play an important role in eliciting immunogenicity and promote natural or therapy-driven anticancer immunosurveillance [15]. It has been shown that necroptotic tumor cells released IL-1α to activate dendritic cells (DCs). Activated DCs induced anti-tumor immunity responses through generating cytotoxic IL-12 or activating $CD8^+$ T cells to eliminate cancer cells [73,74] (Fig. 2).Similarly, Yatim et.al demonstrated that

DAMPs from necroptotic tumor cells elicited robust cross-priming of anti-tumor $CD8^+$ T cells [18]. Furthermore, Prophylactic vaccination of necroptotic CT26 cells efficiently induced maturation of DCs and cross-priming of cytotoxic $CD8^+$ T cells, which serve as potent inducers of adaptive anti-tumor immune responses [75]. NKT cells have also been reported to be involved in RIPK3-mediated anti-tumor immune responses since deletion of RIPK3 impaired activation of NKT cells against tumor [82].

5. Necroptosis in anti-cancer therapy

Triggering apoptosis in cancer cells has been designed and applied to eliminate malignant cells [83]. However, de-regulated apoptotic signaling in cancer, particularly the activation of anti-apoptotic systems, allows cancer cells to escape this program and leads to uncontrolled cell proliferation and tumor survival. Thus, triggering tumor necroptosis, a caspase-independent cell death, holds great therapeutic potential for cancer treatment. So far, several chemotherapeutic agents, natural compounds, and classic necroptosis inducers have been shown to kill cancer cells by inducing MLKL-mediated necroptosis. For example, chemotherapy drugs including etoposide, 5-FU, and cisplatin were able to induce necroptosis of tumor cells when caspase activity was inhibited [84–86]. Poly (I:C), an adjuvant for cancer immunotherapies, has been shown to stimulate RIPK3-mediated necroptosis to elicit potent anti-tumor immunity [73]. Natural compounds shikonin as well as its analogs have been reported to induce necroptosis in glioma and myeloma cells [87,88].

Since one of the hallmarks of cancer is the evasion of apoptosis, triggering necroptosis has become especially important in experimental cancer treatments for apoptosis resistant tumor. It has been shown that overexpression of IAP proteins in cancer cells contributed to the apoptosis resistance and poor prognosis [89]. Necroptosis inducer Smac mimetic BV6 was able to antagonize IAP and induce necroptotic cell death of tumor cells, suggesting an alternative strategy for anti-cancer therapy [90,91]. Cekay et al. identified that synergistic interaction of BV6 with IFNγ induced IRF1-dependent necroptosis in various types of apoptosis-resistant cancer cells when caspase activities was blocked [92]. In pancreatic carcinoma cells and AML cells, BV6 triggers the production of TNFα and formation of necrosome [93,94]. In addition, co-treatment of BV6 and other conventional chemotherapeutic drugs have been also shown to induce necroptosis of cancer cells, such as BV6/Dexamethasone co-treatment in ALL cells, and BV6/Bortezomib co-treatment in NHL cells [95,96].

6. Conclusion and perspectives

Tumor undergoing necroptosis *in vivo* implicates a potential role of necroptosis in modulating cancer development and progression. Recently studies suggest that necroptosis exerts both pro- and anti-tumoral effects during cancer progression. As a pro-inflammatory death mode, necroptotic cells elicit either tumor promoting inflammation or anti-tumor immunity in TME. The intriguing question is how does necroptosis be spatiotemporally regulated to modulate tumor progression and development. In this scenario, identification of molecules released from necroptotic cells and clarification of their functions in tumorigenesis are critical to understand the role of necroptosis in cancer.

The development of therapeutic strategies triggering necroptosis in cancer cells shows great potential for anti-cancer therapy. However, the efficacy and security of these therapeutic strategies need to be widely assessed. It is noteworthy that necroptotic cell death may cause chronic inflammatory responses to promote angiogenesis, cell proliferation, and metastasis. Hence, more experimental and clinical trials are needed to explore the potential application of necroptosis-based anti-cancer therapy.

In summary, accumulating evidence suggests that necroptosis plays a double-edged sword role by having both anti- and pro-tumoral effects during tumor progression. Although several therapeutic strategies have been designed to explore the anti-tumoral efficacy of necroptosis, a deeply understanding of the mechanisms that activate this pathway and its role in tumorigenesis are critical to evaluate the clinical applicability.

Conflict of interest

The author declares no conflict of interest.

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