TOPIC HIGHLIGHT

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Pathophysiological mechanisms of death resistance in colorectal carcinoma

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Abstract

Colon cancers develop adaptive mechanisms to survive under extreme conditions and display hallmarks of unlimited proliferation and resistance to cell death. The deregulation of cell death is a key factor that contributes to chemoresistance in tumors. In a physiological context, balance between cell proliferation and death, and protection against cell damage are fundamental processes for maintaining gut epithelial homeostasis. The mechanisms underlying anti-death cytoprotection and tumor resistance often bear common pathways, and although distinguishing them would be a challenge, it would also provide an opportunity to develop advanced anti-cancer therapeutics. This review will outline cell death pathways (*i.e.*, apoptosis, necrosis, and necroptosis), and discuss cytoprotective strategies in normal intestinal epithelium and death resistance mechanisms of colon tumor. In colorectal cancers, the intracellular mechanisms of death resistance include the direct alteration of apoptotic and necroptotic machinery and the upstream events modulating death effectors such as tumor suppressor gene inactivation and pro-survival signaling pathways. The autocrine, paracrine and exogenous factors within a tumor microenvironment can also instigate resistance against apoptotic and necroptotic cell death in colon cancers through changes in receptor signaling or transporter uptake. The roles of cyclooxygenase-2/prostaglandin E2, growth factors, glucose, and bacterial lipopolysaccharides in colorectal cancer will be highlighted. Targeting anti-death pathways in the colon cancer tissue might be a promising approach outside of anti-proliferation and anti-angiogenesis strategies for developing novel drugs to treat refractory tumors.

Core tip: The mechanisms underlying anti-death cytoprotection and tumor resistance bear common pathways, and although distinguishing them would be a challenge, it would also provide an opportunity to develop advanced anti-cancer therapeutics. Auto-

crine, paracrine and exogenous factors within a tumor microenvironment may instigate apoptotic and necroptotic resistance in colon cancers. The roles of cyclooxygenase-2/prostaglandin E2, growth factors, glucose, and bacterial lipopolysaccharide will be highlighted. Targeting death resistance pathways in colon cancer tissue might be a promising approach outside of anti-proliferation and anti-angiogenesis strategies for developing novel drugs to treat refractory tumors.

INTRODUCTION

Colorectal carcinomas of epithelial origin are characterized by unlimited cell replication, death resistance, and metastasis[1]. In comparison to normal epithelial cells, cancer cells acquire the ability to avoid physiological cell turnover and exhibit an imbalance between renewal and demise, resulting in rapid expansion of tumor mass. It is believed that malignant cells develop adaptive mechanisms for surviving under the extreme conditions of tumor microenvironment, such as restricted oxygen supply and nutrient deprivation. The reprogramming of cancer cells not only contributes to their ability to hyperproliferate but also confers resistance to cell death against endogenous stress and exogenously applied cytotoxic drugs[2]. This review will outline pathways of cell death and discuss how cancer cells manipulate cytoprotective mechanisms to evade it.

MODES OF CELL DEATH

Various types of cell death, *i.e.,* apoptosis, necrosis, and necroptosis, was found in cancer tissues under metabolic stress or cytotoxic stimuli[3]. The signaling pathways of apoptosis and necroptosis will be discussed in the following sections. Although stress stimuli may also induce autophagy which is a catabolic process to remove protein aggregates and damaged organelles for recycling[4], this process is not described in the manuscript here since it may lead to either cell survival or apoptotic death.

Apoptosis

Apoptosis is a type of programmed cell death that is characterized by morphological and ultrastructural changes, including cell shrinkage, membrane blebbing, mitochondrial swelling, and chromatin condensation. Apoptosis may either be initiated extrinsically *via* death receptors such as tumor necrosis factor (TNF) receptor and Fas, or intrinsically *via* mitochondria-

dependent pathways[5] (Figure 1). Moreover, anoikis, which is a form of detachment-induced apoptosis, has been demonstrated to occur in epithelial cells, as they normally require anchorage to basement membranes to establish a monolayer[6].

In the extrinsic apoptotic pathway, the recruitment of cytoplasmic molecules to receptors is initiated following the binding of TNFα or FasL. Docking molecules, including TNF receptor-associated death domain (TRADD), Fas-associated death domain (FADD), procaspase-8/FLICE/MACH, and receptor-interacting protein kinase (RIPK)-1, are recruited to receptor-associated lipid rafts to form a complex that facilitates the cleavage and activation of caspase-8[7,8]. The intrinsic apoptotic pathway occurs following endogenous stress and is associated with a drop in mitochondrial membrane potential. This pathway is regulated by the formation of a mitochondrial permeability transition pore (MPTP), which is composed of Bcl-2 family members and voltage-dependent anion channels on the outer mitochondrial membrane[5,9]. The ratio of Bcl-2 family proteins (*i.e.,* anti-apoptotic Bcl-2 and Bcl-X_L and pro-apoptotic Bax, Bad, Bak, Bid, Bim, and PUMA) is a key factor in determining the conformation of MPTP. Among the Bcl-2 members, Bid can be cleaved by caspase-8 and migrate to the mitochondria in its truncated form tBid to associate with Bax to increase membrane permeability. The drop of mitochondrial membrane potential leads to osmotic swelling of the matrix by water influx and release of cytochrome c from mitochondrial intramembranous space into the cytoplasm, followed by its complex formation with procaspase-9 and APAF-1. The activation of caspase-9 and/or -8 leads to caspase-3 cleavage, endonuclease activation, and ultimately nuclear DNA fragmentation, which is the hallmark of apoptosis[5,9] (Figure 1).

Regulatory proteins, such as FLICE-Like Inhibitory Proteins (FLIPs), inhibit the extrinsic apoptotic pathway by binding to FADD and causing dissociation of the FADD-caspase 8 complex. Additionally, families of inhibitor of apoptosis protein (IAP), including XIAP, cIAP, and survivin, bind to caspase-3 and -9 and thereby inhibit caspase activity. Moreover, XIAP-associated factor 1 (XAF1) negatively regulates the anti-apoptotic function of XIAP[5,9,10].

Necrosis

Necrosis is traditionally known as an uncontrolled form of cell death, characterized by morphological features of mitochondrial swelling, cytoplasmic vacuolation, cytosol density loss, and plasma membrane rupture. The resultant release of subcellular organelles and molecules is considered a potent trigger for tissue inflammation[11].

Necroptosis

A novel form of programmed necrosis, termed necroptosis, has been recently identified. In this pro-
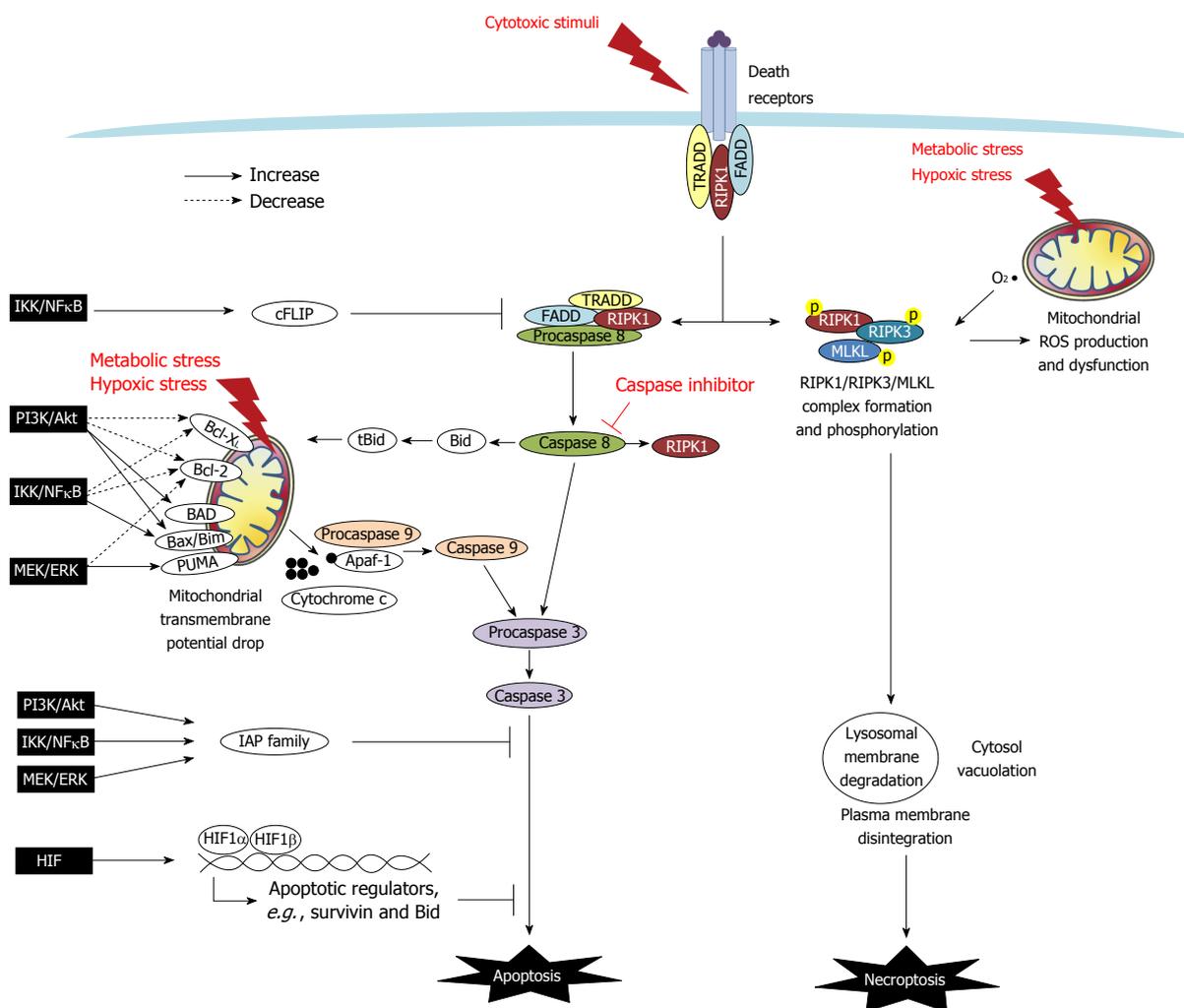
Figure 1 Death resistance signaling in cancer cells. Programmed cell death (*i.e.*, apoptosis and necroptosis) are either triggered extrinsically by cytotoxic stimuli through death receptors, or initiated intrinsically *via* mitochondria dysfunction caused by metabolic and hypoxic stress. In the extrinsic apoptotic pathway, tumor necrosis factor (TNF) or Fas binding to the receptors trigger the recruitment of adaptor molecules to form a death-inducing signaling complex which contains TNF receptor-associated death domain (TRADD), Fas-associated death domain (FADD), procaspase 8/FLICE, and receptor-interacting protein kinase 1 (RIPK1) to facilitate the activation of caspase 8. Caspase 8 then cleaves and activates caspase 3 (the final caspase in the apoptotic pathways), and it also truncates Bid and RIPK1. The intrinsic apoptotic pathway is associated with mitochondrial dysfunction. The ratio of Bcl-2 superfamily proteins, including anti-apoptotic Bcl-XL and Bcl-2, and pro-apoptotic Bad, Bid, Bax, Bim and PUMA, determines the formation of the mitochondrial permeability transition pore. The truncated form tBid cleaved by caspase-8 can migrate to the mitochondria to associate with Bax to increase membrane permeability. The drop of mitochondrial transmembrane potential leads to osmotic swelling and release of cytochrome c to complex with Apaf-1 and procaspase 9 which undergo cleavage into the active form of caspase 9. Caspase 9 and/or caspase-8 activates caspase-3, and ultimately leads to nuclear DNA fragmentation. Moreover, FLICE-like proteins (FLIP) and inhibitors to apoptosis proteins (IAPs), including cIAP, survivin and XIAP, provide a brake on the apoptotic cascade. In cancers, signaling pathways such as PI3K/Akt, MEK/ERK, IKK/IκB/NFκB and HIF regulate apoptosis by modulating Bcl-2 members and altering expression of FLIP and IAPs. In the extrinsic necroptotic pathway, stimulus of TNFα in the presence of a caspase inhibitor frees RIPK1 to form a complex with RIPK3 for auto- and trans-phosphorylation, which then recruits and phosphorylates MLKL. The RIPK1/RIPK3/MLKL complex causes mitochondrial dysfunction and executes subcellular features of necroptosis, such as lysosomal membrane degradation, cytosol vacuolation, plasma membrane disintegration, and ultimately cellular explosion. In the intrinsic necroptotic pathway, metabolic and hypoxic stress induces the mitochondrial production of reactive oxygen species (ROS) such as superoxide, which subsequently leads to RIPK1/3 activation and the final steps of necroptosis. However, signaling pathways to regulate necroptosis has not yet been reported.

cess, signaling pathways involving RIPK1/RIPK3-mediated phosphorylation activate the mixed lineage kinase domain-like protein (MLKL) to execute the final step of cell destruction[11] (Figure 1). The best defined necroptosis pathway was elucidated following the stimulation of cells with TNFα in the presence of ZVAD (a pan-caspase inhibitor)[11,12]. This observation has led to the development of a preliminary hypothesis that necroptosis may be a default mechanism for cells that are unable to die *via* apoptosis[12,13]. However,

with increasing evidence of instances of necroptotic death occurring following various stimuli (*e.g.,* oxygen and glucose deprivation, extensive DNA damage, hyperactivation of Poly(ADP-ribose)polymerase -1 (PARP), and free radical exposure), it is now clear that RIPK1/3-dependent necrosis is an independent mode of cell death that shares common pathways with apoptosis[14,15].

Early studies of necroptotic pathways by activating TNF receptor in the presence of caspase inhibition

demonstrated that the adapter molecules FADD and TRADD recruited RIPK1, which subsequently undergo a series of ubiquitination and deubiquitination events before RIPK1 forming a complex with RIPK3 and MLKL in the cytosol for auto- or trans-phosphorylation[16]. The RIPK1/RIPK3/MLKL kinase complex has been proposed to mediate necrotic death *via* the induction of mitochondrial dysfunction[16]. Additionally, mitochondria-derived free radical production and lysosomal membrane disintegration have been reported to be facets of necroptotic machinery[17]. Free radical scavengers that suppress mitochondrial reactive oxygen species (ROS) were shown to inhibit the execution of necroptotic death induced by TNF and hypoxic stress, but had no effect to necroptosis induced by PARP[18,19]. Other reports revealed that hypoxia-induced mitochondrial ROS was upstream of RIPK1/RIPK3 activation in the necroptotic signaling pathway[19]. The order of intracellular events leading up to plasma membrane explosion and intracellular content spilling may vary depending on trigger type[17-19]. Overall, it is currently recognized that two modes of cell death are driven by RIPK1 through its kinase function, including apoptosis *via* its formation of a complex with caspase-8/FADD/TRADD and necroptosis *via* its formation of a complex with RIPK3/MLKL (Figure 1).

APOPTOSIS IN NORMAL COLON AND COLORECTAL CANCERS

Physiological cell turnover in intestine

The intestinal epithelial monolayer is maintained in a state of dynamic equilibrium that is governed by the balance between crypt proliferation and surface/villus shedding and cell death. Newly proliferated cells that are derived from stem cells in the crypts migrate upward and differentiate into various cell types (*e.g.*, absorptive and secretive epithelial cells, goblet cells, and endocrine cells); the cells then undergo detachment and apoptosis at an "extrusion zone" on the luminal surface with a turnover rate of 5-7 d[20,21]. Epithelial integrity and intestinal homeostasis are tightly controlled by the balancing of two physiological processes, namely cell proliferation and death.

Inverse correlation between epithelial apoptosis and colon tumor susceptibility

Progressive inhibition of cell apoptosis has been associated with the transformation of normal colorectal epithelium into carcinoma[22]. Direct evidence of an inverse correlation between epithelial cell death and tumor susceptibility has been provided in recent studies. Mice that were deficient in pro-apoptotic molecules (*e.g.,* Bak and Fas) displayed a higher incidence and higher numbers of aberrant crypt foci and colorectal tumors following induction with the carcinogen azoxymethane (AOM) or AOM/dextran sulfate sodium (DSS)[23,24]. Although a lack of Bak or

Fas did not affect physiological apoptosis in colon cells, a decreased level of epithelial cell death was observed following exposure to pro-apoptotic triggers (*e.g.,* gamma-radiation and genotoxic carcinogens)[23,24]. Moreover, PUMA-knockout mice exhibited reduced apoptosis in colonic crypts and increased colonic tumor susceptibility following an AOM/DSS challenge. A deficiency of PUMA enhanced the formation of spontaneous adenomas in the distal small intestines and colons of APC(Min/+) mice[25]. These studies indicate that cells that are unable to undergo apoptosis partly contribute to cancer progression.

ANTI-DEATH CYTOPROTECTIVE STRATEGIES IN NORMAL INTESTINE

Surface epithelial layers are constantly bombarded by orally acquired harmful substances and luminal bacteria, and are also exposed to potentially hypoxic conditions due to their location at the end of a capillary circuit that interfaces with an anaerobic lumen. When exposed to intrinsic stress or external stimuli, a normal epithelium exhibits excessive cell death (*i.e.,* apoptosis, necrosis and necroptosis) and display barrier defects. However, cytoprotective strategies against cell death also exist to maintain gut homeostasis.

The cellular survival strategies include uptake of glucose and glutamine, free radical scavenging, transcriptional adaptation, and paracrine effects induced by cyclooxygenase (COX)-2/prostaglandin E2 (PGE2). In the following sections of this work, several facets of anti-death cytoprotective strategies that share common pathways to tumor resistance will be discussed. Understanding the similarity between epithelial cytoprotection and cancer resistance would help to identify distinct mechanisms undertaken by tumor cells for the search of advanced therapeutic targets.

One of the unique characteristic of the intestinal tract is that it possesses dual routes of nutrient supply, including hematologic and dietary sources. In small intestinal epithelium, apical glucose uptake is mediated by sodium-dependent glucose transporter 1 (SGLT1), while glucose transporter 2 (GLUT2) facilitates diffusive transport of intracellular glucose across the basolateral membrane and into the bloodstream[26]. Large intestinal epithelium normally expressed GLUT5 and GLUT6, but not the other glucose transporters[27]. We and others have previously shown that enhanced glucose uptake *via* SGLT1 can protect intestinal epithelial cells against various pro-apoptotic triggers, such as mesenteric ischemia/reperfusion, microbial challenges, and endotoxemia[28-31]. Energy production has been generally assumed as the main cytoprotective mechanism of glucose uptake; however, alternative pathways of SGLT1-mediated activation of phosphatidylinositide 3-kinase (PI3K)/Akt and nuclear factor kappa B (NFκB) pathways also partially contributes to cytoprotection[28,31]. Other than glucose,

glutamine (a non-essential amino acid) is important for cell survival during conditions of stress. Glutamine can prevent epithelial cell apoptosis caused by hypoxia/reoxygenation, oxidants, endotoxins, heat stress, and TNFα[32-36]. The inhibition of gut epithelial cell apoptosis by glutamine is mediated through upregulation of autophagy and increased transcription of heat shock proteins[34,35,37].

Redox enzymes, including catalase (CAT), super-oxide dismutase (SOD), glutathione reductase, and glutathione-S-transferase, suppress intracellular accumulation of free radicals. An intracellular redox system converts highly reactive free radicals, such as superoxide, hydrogen peroxide, and hydroxyl radical, into lower energy molecules. Intravenous injections of CAT and SOD have been shown to decrease intestinal inflammation and epithelial barrier dysfunction in animal models of mesenteric ischemia/reperfusion injury[38-40].

Hypoxia-inducible factor (HIF) is a transcription factor that is activated in epithelial cells under the low oxygen conditions of ischemic or inflamed gut[41,42]. The HIF family includes three proteins: HIF-1, HIF-2, and HIF-3. Activation of HIF is dependent on the stabilization of the oxygen-sensitive α subunit, which is subsequently translocated to the nucleus to form a functional complex with the β subunit and various other coactivators[43]. HIF-1α/2α forms a dimeric complex with HIF-1β, and triggers transcription by binding to the hypoxia response element of various gene promoter regions[44,45]. Under normoxic conditions, the hydroxyl hydroxylase (PHD)-mediated hydroxylation of proline residues on HIF-1α/2α leads to its ubiquitination and degradation. Low oxygen levels have been shown to result in a downregulation of PHD activity and to stabilize HIF-1α/2α levels[43]. HIF-1 activation has been implicated in maintaining epithelial barrier protection in models of intestinal ischemia/reperfusion, experimental colitis with inflammatory hypoxia, and in mouse ileal loops after exposure to bacterial toxins[41,42,46-48].

Cyclooxygenase (COX)-2, a catalyzing enzyme for PGE2 production, is involved in increased vascular permeability and blood flow during inflammation and wound healing. COX-2 also protects against colonic epithelial damage in animal models of chemical-induced colitis[49,50]. Oral supplementation of PGE2 increased proliferation and reduced apoptosis of intestinal epithelium in mice with colitis[49]. Moreover, PGE2 increased c-IAP2 expression in normal rat epithelial cells[51].

The detailed anti-death signaling pathways have primarily been delineated from observations made in adenocarcinoma cell line studies, and they will be discussed in the context of cancer cell death resistance in the next section.

INTRACELLULAR MECHANISMS OF DEATH RESISTANCE IN CANCERS

Death and anti-death signaling in cancer cells has been extensively studied in the context of cell survival against exogenously applied cytotoxic drugs. Substantial efforts have also been made to uncover the pathways that lead to cancer cell death and survival under conditions of endogenous metabolic stress, with the goal of learning how to therapeutically manipulate tumor-specific machinery to produce anti-cancer effects. We will highlight the mechanisms of death resistance in cancer cells against exogenous or endogenous stress. These intracellular pathways include direct alteration of death machinery and modulation of upstream events such as tumor suppressor gene inactivation and pro-survival signaling. For additional discussion of drug-related resistance mechanisms, such as efflux pumps and enzymatic degradation, please see other review articles[52,53].

Direct alteration of apoptotic and necroptotic regulators in cancer

Defects in apoptotic signaling and increased use of anti-apoptotic pathways have been reported in colon cancer cells. Key regulatory proteins of apoptotic machinery, such as families of Bcl-2 and IAP, undergo changes in expression during the transition of an adenoma into a carcinoma and have therefore been utilized as prognostic biomarkers[54,55]. An overexpression of the anti-apoptotic Bcl-2 family member Bcl-X$_L$ is a known predictor of poor prognoses in patients with colonic adenocarcinomas[56]. Increased expression levels of anti-apoptotic regulators such as c-FLIP, XIAP, cIAP2, and survivin have also been correlated with disease progression and poor survival in colon cancer patients[57-61]. A recent report indicated that expression levels of the necroptotic adaptors RIPK1 and RIPK3 are significantly decreased in human colon cancer tissues compared to adjacent normal mucosa[62]. Overall, an increase of anti-apoptotic molecules and a decrease in pro-necroptotic kinases are both likely to contribute to death resistance in cancer cells (Table 1). The resistance mechanisms that occur upstream of the alteration of apoptotic regulators are further discussed below.

Inactivation of tumor suppressor genes to prevent apoptosis in cancer

Mutations in oncogenes (RAS and β-catenin) and tumor suppressor genes (p53 and APC) have been identified to arise throughout the course of tumorigenesis[63]. The intriguing field of oncogene mutation and cell hyperproliferation has been reviewed comprehensively[64] and will not be discussed here. Instead, cancer cell death resistance that is imparted by mutation of the p53 tumor suppressor gene and the resultant functional consequences of this resistance will be the focus of this section.

Mutations in the p53 gene occur in half of all co-lorectal cancer cases and have been correlated with adenoma-to-carcinoma transitions and aggressive subsets of colorectal cancer[65,66]. Tumor cells harboring

Table 1 Alteration of apoptotic and necroptotic regulators in human colon cancers			
Classification	**Molecule**	**Expression in cancer tissues**	**Ref.**
Bcl-2 family	Bcl-X$_L$	Increased	[56]
IAP family	cFLIP	Increased	[57]
	cIAP2	Increased	[59,60]
	survivin	Increased	[55,61]
	XIAP	Increased	[58]
RIP kinase family	RIPK1/RIPK3	Decreased	[62]

IAP: Inhibitor of apoptosis protein; FLIP: FLICE-like inhibitory protein; XIAP: X-linked IAP; RIP: Receptor-interacting protein.

p53 mutations have long been known to be defective in the induction of apoptosis[67]. In addition to its pro-apoptotic role, it has become evident that p53 acts as a multifunctional transcription factor and is involved in physiological cellular responses to stressful stimuli (*e.g.,* DNA damage and hypoxia), surveillance mechanisms that cause cell cycle arrest following cellular damage or oncogenic aberration, and regulation of metabolic pathways for a switch from glycolysis to oxidative phosphorylation[68,69]. The molecular mechanisms that are employed by p53 to induce cell death in the context of suppressing cancer progression include the transcriptional regulation of pro-apoptotic PUMA expression, the generation of oxidative free radicals within mitochondrial components, the reduction of COX-2/PGE2 synthesis, and the induction of death receptor 5[70-73].

Signaling pathways that modulate apoptotic regulators in cancer

A number of signaling molecules and transcription factors are involved in the dysregulation of death machinery in cancer cells (Figure 1). These include the PI3K/Akt, mitogen-activated protein kinase kinase (MEK)/extracellular signal-regulated kinase (ERK), IκB kinase (IKK)/inhibitor of NFκB (IκB)/NFκB, and HIF signaling pathways (Table 2).

Studies on colon cancer cell lines have shown that an upregulation of PI3K/Akt protein kinases has been associated with increased expression of anti-apoptotic Bcl-2 proteins (*e.g.,* Bcl-2, Bcl-X$_L$, and survivin)[74,75], phosphorylation and inactivation of pro-apoptotic Bad and Bax[76-78], and activation of XIAP[79]. In colon cancer and epithelial cells, the MEK/ERK signaling pathway mediates the phosphorylation and stabilization of Bcl-2[80], the inactivation of Bax and the degradation of Bim[78,81], the suppression of PUMA induction[73], the downregulation of XAF1 and the upregulation of XIAP expression[82].

The activation of the IKK/IκB/NFκB pathway, which serves as a putative proinflammatory signal, has been linked with anti-apoptotic effects in normal colonocytes and colon cancers alike. The activation of the IκB kinase complex (IKKα/β/γ) leads to the phosphorylation of NFκB-bound IκB and causes

Table 2 Signaling pathways for modulation of apoptotic regulators in cancer		
Pathway	**Observation in experimental models**	**Ref.**
PI3K/Akt	Increase of Bcl-2, Bcl-X$_L$ and survivin expression in colon cancer cell lines (SW480, SW620, HCT116, and HT29)	[74,75]
	Inactivation of BAD by phosphorylation in colon cancer cell lines (HT29 and H508)	[76,77]
	Decreased expression of Bim and inactivation of Bax in colon cancer cell lines (HCT116 and DLD1), and increase of tumor growth in xenograft models	[78]
MEK/ERK	Phosphorylation and stabilization of Bcl-2 in colon cancer cell lines (HCT116 and HT29) for increase of anoikis, and promotion of metastasis in xenograft models	[80]
	Decreased expression of Bim and inactivation of Bax in colon cancer cell lines (HCT116 and DLD1), and increase of tumor growth in xenograft models	[78]
	Suppression of PUMA expression and activity in colon cancer cell lines (Lovo and SW1116)	[73]
	Dowregulation of XAF1 and upregulation of XIAP in colon cancer cell lines (HCT116, Lovo, DLD1, and SW1116)	[82]
IKK/IκB/ NFκB	Induction of cIAP-2 expression in colon cancer cell lines (Caco-2, HCT116, KM20, and KM12C)	[91]
	Increase of Bcl-2, Bcl-X$_L$, and cFLIP in colon cancer cell lines (COLO205 and HCT116)	[92]
HIF	Binding to hypoxia-responsive element of the Bid promoter in colon cancer cells (SW480) for Bid downregulation	[94]
	Binding to hypoxia-responsive element of the survivin promoter in breast cancer cells (MCF-7) for survivin upregulation	[93]

PI3K: Phosphatidylinositide 3-kinase; MEK: Mitogen-activated protein kinase kinase; ERK: Extracellular signal-regulated kinase; NFκB: Nuclear factor kappa B; IκB: Inhibitor of NFκB; IKK: IκB kinase; HIF: Hypoxia-inducible factor.

IκB to undergo ubiquitin-dependent degradation, enabling the liberated NFκB to translocate to the cell nucleus and act as a transcription factor[83]. Unlike other subunits in the complex, IKKα can shuttle between the nucleus and cytoplasm to facilitate NFκB-regulated gene expression[84]. An elegant study indicated that either epithelial-specific ablation of IKKγ (also called NEMO) or a deficiency of both IKKα and IKKβ can lead to increased levels of apoptosis in mouse colonocytes[85]. Using carcinogen-induced colon cancer models, epithelial-specific IKKβ-KO mice were shown to exhibit increased colonic cell apoptosis associated with a reduction of tumor growth compared to wild type mice[86]. Numerous studies of colonic, gastric and esophageal cancer cell lines have demonstrated that blocking NFκB-induced apoptosis under baseline conditions sensitizes cells to treatment with 5-fluorouracil (5-FU)[87-89]. The underlying mechanisms of this phenomenon included IKKα-mediated phosphorylation of CREB binding protein (a transcriptional coactivator), which induced a switch in binding preference from p53 to NFκB and led to a concurrent upregulation of NFκB-dependent anti-apoptotic genes, and the downregulation of p53-

mediated pro-apoptotic genes[90]. Moreover, in colon cancer cells, the transcriptional targets of NFκB include the anti-apoptotic regulators Bcl-2, Bcl-X$_L$, cFLIP and IAP[91,92].

HIF is upregulated in the hypoxic core of rapidly growing solid tumors and is therefore considered a biomarker of poor prognosis in colon cancer patients[45]. HIF-1 targets promoter sites of apoptotic regulators such as survivin and Bid, and directly modulates cell death pathways[93,94]. Other HIF-1-targeted genes included trefoil factor[47], COX-2[95], glucose metabolic enzymes [*e.g.,* hexokinase (HK), glyceraldehyde-3-phosphate dehydrogenase (GAPDH), pyruvate kinase (PK), pyruvate dehydrogenase kinase (PDK)], and glucose transporters (*e.g.,* GLUT-1 and -3)[45,96,97]. HIF-1α also directly activates promoter regions of various growth factors and receptors, including vascular endothelial growth factor (VEGF), c-Met [a receptor for hepatocyte growth factor (HGF)], HGF activator[98-100]. Moreover, several reports have shown that HIF-2α increases transcriptional and translational expression of amphiregulin [a member of the epidermal growth factor (EGF) family] and EGF receptor (EGFR), and favors autocrine growth signaling in various types of cancer[101-103].

TUMOR MICROENVIRONMENT CAUSES DEATH RESISTANCE IN COLON CANCER

Autocrine, paracrine and exogenous factors in tumor microenvironments also instigate resistance against apoptotic and necroptotic cell death in colon cancers *via* changes in receptor signaling and transporter uptake (Figure 2). The roles of COX-2/PGE2, growth factors, glucose, and bacterial LPS are highlighted below.

COX-2/PGE2-mediated apoptotic resistance in cancer

Increased expression of COX-2 was observed in colon adenocarcinoma, and is considered one of the earliest events in tumor development[104,105]. Clinical studies have provided strong evidence that long term use of non-steroidal anti-inflammatory drugs reduce the incidence of colon cancers[106]. Various mechanisms have been proposed for the COX-2-mediated tumor-promoting activity, including increased blood flow, induction of growth factors, increase of cell proliferation, or modulation of apoptotic regulators[51,107,108]. COX-2/PGE2 induces synthesis of amphiregulin and activation of EGFR signaling in colon cancer cell lines[107,108]. Moreover, stimulation with PGE2 was found to suppress Fas-induced apoptosis in colon cancer cells *via* upregulation of IAP expression[51] (Figure 2).

Growth factor-dependent apoptotic and necroptotic resistance in cancer

A number of growth factors have been associated with death resistance in cancer, including epidermal, hepatocyte, and insulin-like growth factors (Figure 2). EGFR activation has long been known to induce epithelial cell proliferation, restitution, and tumorigenesis. In colorectal and gastric cancer cells, EGFR activation also exerts anti-apoptotic effects that are mediated by PI3K/Akt, ERK and IκBα/NFκB signaling, and protects cancer cells against anoikis and enhances epithelial-mesenchymal transition[109-112]. Moreover, both EGFR and its downstream Akt and ERK pathways are known to be involved in preventing apoptosis in stem-like cell populations in serum-deprived colorectal cancer cells[113]. A positive feedback loop between EGFR and HIF signaling pathways may also contribute to the increase of death resistance in cancer, as revealed by evidence that EGFR activation leads to increased expression and nuclear translocation of HIF-1α/1β in normoxic conditions[93,95,114]; furthermore, HIF-2α increases the transcript and protein expression of EGFR and amphiregulin[101-103]. Recent evidence has revealed a co-expression of EGFR and SGLT1 in human colorectal and oral squamous carcinoma[115,116]. Interactions between EGFR and SGLT1 have shown a positive correlation with cancer cell proliferation and survival through a mechanism that involves the stabilization of membranous SGLT1 proteins by EGFR in a tyrosine kinase-independent manner[117,118].

Elevated expression of the HGF receptor Met has been shown in human colorectal cancers compared to normal mucosa[119]. Recently, both the autocrine production of HGF and a positive feedback loop that was mediated by a constant activation of the HGF gene promoter due to microsatellite instability that was characterized by truncations of the promoter region were found in human colon carcinoma samples and cell lines[120]. Activation of HGF/Met signaling was shown to cause a downregulation in the expression of RIPK1 proteins, which correlated with a reduction in the number of necroptotic regions found in colon tumors[120]. Moreover, evidence of HIF-1α directly activating the promoter regions of Met and HGF activator (a serine protease that converts HGF to its active form) was found in pancreatic cancer and glioma cells[99,100]. Interestingly, increased activation of Met was found to be induced in human carcinoma Caco-2 cells following treatment with cetuximab (an EGFR inhibitor), which served as a chemoresistance mechanism[121].

Colon cancers express high levels of both insulin-like growth factor 1 (IGF1) and its receptor compared to normal mucosa. The overexpression of IGF1 receptors in human colon cancer cells was found to confer resistance to serum-deprivation induced apoptosis, which was associated with increased activation of Akt and an upregulation of Bcl-X$_L$[122]. Another report demonstrated that inhibition of the IGF1 receptor sensitized human colon adenocarcinoma cells to cetuximab and restored cell death in drug-resistant cell clones[123].
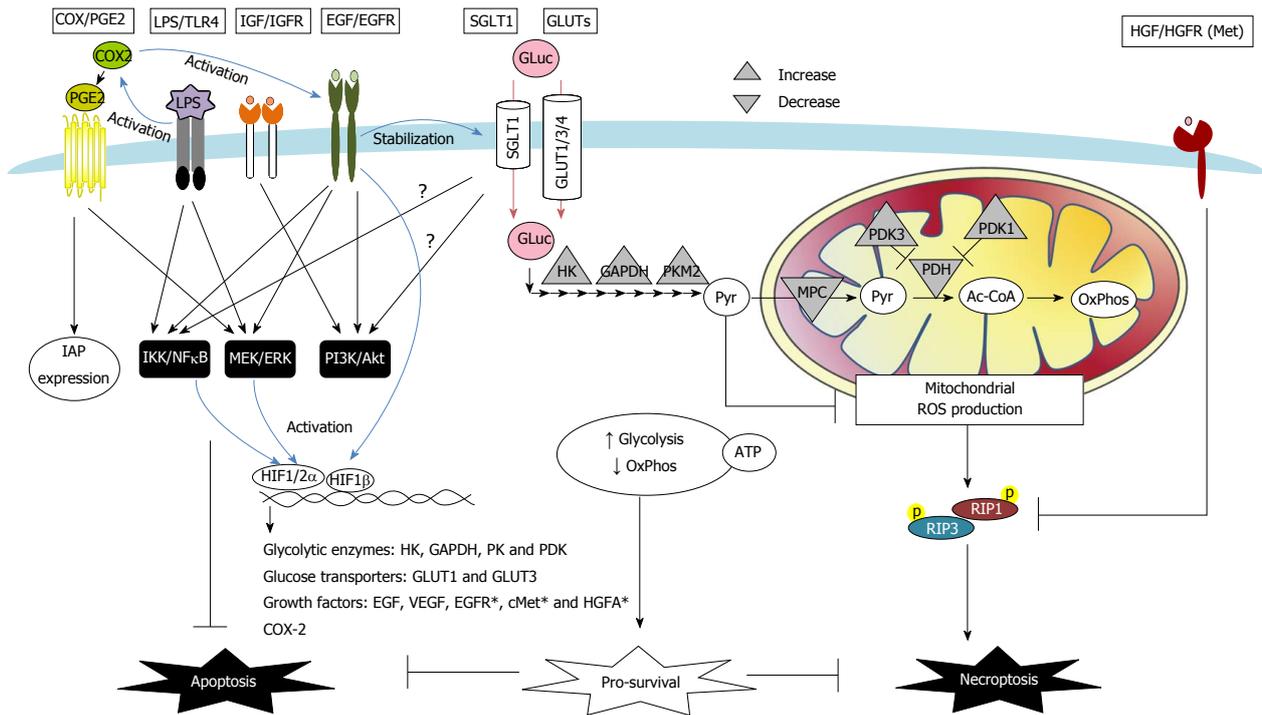
Figure 2 Proposed schema of death desistance mechanisms *via* modulation of receptor signaling and transporter uptake in colon cancer cells. A number of autocrine, paracrine, or exogenous factors instigate death resistance in colon carcinoma. These pathways included cyclooxygenase (COX)-2/prostaglandin E2 (PGE2), bacterial lipopolysaccharide (LPS)/Toll-like receptor 4 (TLR4), growth factors [*i.e.*, insulin-like growth factor (IGF), epidermal growth factor (EGF), and hepatocyte growth factor (HGF)], as well as glucose transport and metabolism. COX/PGE2 upregulates the IAP expression and activates EGF/EGFR signaling to inhibit apoptosis in colon cancer cells. TLR4 antagonizes cell apoptosis caused by its co-receptor CD14, induces anti-apoptotic MEK/ERK and IKK/IκB/NFκB signaling, and activates COX-2 pathways in colon carcinoma. Growth factors such as IGF and EGF induce anti-apoptotic PI3K/Akt, MEK/ERK, and IKK/IκB/NFκB pathways in colon cancers. Moreover, activation of HGF and its receptor Met renders colon cancer cells resistant to necroptosis *via* downregulation of RIPK1 protein expression. Alteration of transport and metabolism of glucose (Gluc) is another survival strategy of cancer cells. Abnormally expressed sodium-dependent glucose transporter 1 (SGLT1) and GLUT1/3/4 enhance glucose uptake in colon carcinoma. Activation of SGLT1 induces PI3K/Akt and IKK/IκB/NFκB pathways in normal intestinal epithelial cells; however, their roles in anti-death mechanisms of colon cancers remain unclear (?). Increased glycolysis and decreased mitochondria-dependent oxidative phosphorylation (OxPhos) are commonly seen in cancer cells. The metabolic shift results from upregulated expression of glycolytic enzymes for increased (Pyr) production [*e.g.*, hexokinase (HK), glyceraldehyde-3-phosphate dehydrogenase (GAPDH), pyruvate kinase (PK)], and also from downregulated expression of mitochondrial pyruvate carrier (MPC) and pyruvate dehydrogenase (PDH) that limits pyruvate conversion to Acetyl Co-A (Ac-CoA). The metabolic shift and predominantly glycolytic ATP generation are adaptive responses to hypoxic stress and promotes cancer cell survival. The final glycolytic product pyruvate, which is also a free radical scavenger, prevents hypoxia-induced necroptotic death in colon cancer cells *via* suppression of mitochondrial ROS. Hypoxia acts a stressor but also a death regulator by HIF-dependent transcription of a number of genes, including glucose metabolic enzymes [*e.g.*, HK, GAPDH, PK, and pyruvate dehydrogenase kinase (PDK)], glucose transporters (*e.g.*, GLUT-1 and GLUT-3), and growth factors [*e.g.*, EGF and vascular endothelial growth factors (VEGF)]. Other HIF-targeted genes, *e.g.*, EGFR, cMet, and HGF activator (HGFA), were reported on non-intestinal cancer cells (*), and may also contribute to the death resistance mechanisms. Lastly, EGF activates HIF signaling in normoxic conditions, leading to a positive feedback loop of adaptation fueling anti-death and pro-proliferative cancer growth.

Glucose-dependent apoptotic and necroptotic resistance in cancer

Increased glucose dependency and altered glucose metabolism are associated with cancer cell transformation (Table 3). In normal cells, one glucose molecule is catalyzed into two ATPs and two pyruvate molecules in an anaerobic fashion by a cascade of glycolytic enzymes, including HK, GAPDH, and PK[124]. The final glycolytic product, pyruvate, is transported across the inner mitochondrial membrane (IMM) by mitochondrial pyruvate carrier (MPC) and is then converted to acetyl-CoA by pyruvate dehydrogenase (PDH) before entering into the tricarboxylic acid (TCA) cycle that occurs in the mitochondrial matrix[125,126]. A reduced substrate is generated by the TCA cycle and is then fed into the electron transport chain of the IMM, after which oxidative phosphorylation leads to the production of 36 ATPs. In contrast to normal cells, tumors exhibit high levels of glycolysis despite the presence of sufficient oxygen, which is a phenomenon known as the Warburg effect[127].

The abnormal expression of the GLUT isoforms 1, 3, and 4 and the SGLT1 protein have been widely documented in studies of human colon cancer samples[27,115,116,128-130]. A large body of evidence indicates that the upregulation of GLUT1 and several glycolytic enzymes is dependent on the transcriptional activity of HIF-1 in both human colon cancer tissues and drug-resistant cancer cell lines[96,131-133]. Recent studies have indicated that the stabilization of membrane SGLT1 expression in colon cancer cells is dependent on EGFR activation[117,134], suggesting that this pro-proliferative and anti-apoptotic growth factor is also involved in the mechanism that underlies enhanced glucose uptake (Figure 2).

Changes in glucose uptake and metabolism have

Table 3 Glucose-dependent mechanisms in death resistance of colon cancer

Classification	Molecule	Expression and mechanism	Ref.
Glucose uptake			
Transporters	GLUT1	Abnormal expression of GLUT1 in colon cancer	[128,129]
		Hypoxia-induced expression of GLUT1 by HIF-1 binding to the GLUT1 promoter	[96,131,132]
		GLUT1-mediated glucose uptake promoted drug resistance in colon cancer cells	[136]
	GLUT3,4	Abnormal expression of GLUT3,4 in colon cancer	[19,27,130]
	SGLT1	Abnormal expression of SGLT1 in colon cancer	[27,115]
		Stabilization of membrane SGLT1 expression is dependent on EGFR in a kinase-independent mechanism	[117,134]
Glucose metabolism			
Enzymes	PK	Upregulation of PKM2 isoform in chemoresistant cancer cells	[132]
	PDK-1	PDK-1 as a novel Wnt target gene improved colon cancer cell survival via enhancement of glycolysis	[142]
	PDK-3	HIF1-mediated upregulation of PDK-3 inhibited mitochondrial phosphorylation and promoted drug resistance	[143]
	HK, GAPDH	HIF1-dependent transcriptional upregulation	[45,96]
	PDH	Decreased expression in colon cancer cells	[141]
Carriers	MPC	Reduction of MPC activity promoted glycolysis and maintenance of stemness properties	[144]
Products	ATP	Elevation of intracellular ATP promoted cancer cell survival and induced drug resistance	[145,146]
	Pyruvate	Pyruvate prevented hypoxia-induced necroptosis through suppression of mitochondrial free radicals in an ATP-independent mechanism	[19]

GLUT: Glucose transporter; SGLT1: Sodium-dependent glucose transporter 1; EGFR: Epidermal growth factor receptor; PK: Pyruvate kinase; PDK: Pyruvate dehydrogenase kinase; HK: Hexokinase; GAPDH: Glyceraldehyde-3-phosphate dehydrogenase; PK: Pyruvate kinase; PDH: Pyruvate dehydrogenase; MPC: Mitochondrial pyruvate carrier.

been suggested to provide a survival advantage to tumor cells and also to contribute to anti-cancer drug resistance. A previous report has shown that high glucose levels can modulate the cytotoxicity and anti-proliferative effects of 5-FU in colon cancer cell lines[135]. The *in vitro* inhibition of GLUT1-mediated glucose uptake by phloretin was found to sensitize colon cancer cells to overcome apoptotic resistance to daunorubicin under conditions of hypoxia[136]. The modulation of glucose metabolic pathways by chemicals (*e.g.,* 3-bromopyruvate, iodoacetate, dichloroacetate, or 2-deoxyglucose) was found to attenuate 5-FU resistance in colonic and gastric cancer cells[137-139]. Recent studies have indicated that high levels of intracellular glucose lead to an increased side population (SP) of stem-like cells within the overall cancer cell population; these cells exhibit high glycolytic activity and drug export ability, and are most resistant to cell death[140]. The underlying mechanism of SP cell expansion involves glucose-mediated suppression of AMP-activated protein kinase and an activation of Akt signaling[140].

PK is the final rate-limiting enzyme in the glycolytic pathway, and it catalyzes the conversion of phosphoenolpyruvate and ADP into pyruvate and ATP. PDH, which converts pyruvate into acetyl-CoA, can be phosphorylated and inactivated by PDK in physiological conditions. The PK isoform M2 (PKM2) is significantly upregulated in 5-FU-resistant colon cancer cell lines[132]. Moreover, decreased expression of PDH was reported in colorectal cancer cells[141]. A recent study has identified that PDK-1 is a novel Wnt target gene that can promote glycolysis and colon cancer cell survival[142]. Hypoxia-induced PDK-3 expression

via the activation of HIF-1 has been shown to lead to an inhibition of mitochondrial phosphorylation and the promotion of drug resistance[143]. Additional research has indicated that reduced MPC activity promotes glycolysis and the maintenance of stemness in colon cancer cells[144].

ATP has generally been assumed to be the effector of glucose metabolism that promotes cancer growth, survival, and chemoresistance. A number of studies have shown that depleting ATP *via* glycolytic inhibition increases apoptosis in multidrug- resistant cancer cells under both normoxic and hypoxic conditions[145,146]. Moreover, direct delivery of liposome-encapsulated ATPs was found to be sufficient for promoting survival and inducing resistance to oxaliplatin in formerly drug-sensitive colon cancer cells[146]. Whether ATP-dependent chemoresistance is a result of cell hyperproliferation or the induction of anti-death mechanisms remains unknown.

It is notable that an energy-independent mechanism is also involved in glucose-mediated death resistance in cancer cells. Pyruvate not only serves as a link between glycolysis and mitochondrial respiration but also acts as a scavenger for oxidative free radicals through a non-enzymatic reaction[147]. Our recent studies have shown that pyruvate (uncoupled to ATP) plays a distinct role in promoting cancer cell survival[19]. Glycolytic pyruvate prevented RIPK1/3-dependent necroptosis caused by hypoxic stress in colon cancer cells through the suppression of mitochondrial free radicals[19]. Collectively, the manipulation of glucose uptake and metabolic pathways in conjunction with the application of cytotoxic drugs may promote anticancer effects and overcome chemoresistance (Figure 2).

With an increasing body of evidence suggesting that chemoresistance in colon cancers can be mediated by glucose, it is notable that dietary glutamine supplementation was shown to reduce tumor burden by increasing apoptosis and decreasing proliferation in the colons of mouse models that were submitted to colitis-associated cancer induction[148]. Although a glutamine-dependent chemopreventive effect on tumorigenesis was suggested to result from its anti-inflammatory activity, it remains unclear whether glutamine metabolism by first pass in epithelial cells (in place of glucose metabolism) may play a role in tumor suppression. The differential roles of glucose- and glutamine-dominant metabolism in the regulation of tumorigenesis warrant further investigation.

Bacterial LPS/Toll-like receptor 4-dependent apoptotic resistance in cancer

The innate immune receptor Toll-like receptor 4 (TLR4) forms a complex with CD14 and MD2 for sensing bacterial LPS. This receptor complex was originally identified on monocytes/macrophages and endothelial cells that are responsible for septic shock. Given the juxtaposition of commensal bacteria and intestinal mucosa, it had been assumed that normal gut epithelial cells were not equipped with LPS receptors. However, accumulating data showed that normal human colonocytes constitutively express CD14 in the absence of TLR4, and a strong immunoreactivity of CD14 and TLR4 was found in human colorectal carcinoma tissues, indicating a link between LPS/TLR4 signaling and tumor formation[149-151].

The activation of TLR4 signaling may contribute to tumorigenesis by promoting epithelial proliferation and/or by reducing cell death (Figure 2). *In vitro* studies in colon adenocarcinoma cell lines have demonstrated that LPS/TLR4 induced resistance to apoptosis *via* NFκB and ERK signaling, without modulating the rate of cell division[152,153]. Conversely, several studies have revealed enhancement of both cell *via*bility and proliferation following the activation of LPS/TLR4 in cancer cell lines[154,155]. Using chemically induced colitis-associated mouse cancer models, numerous studies have shown that the genetic absence of TLR4 and its downstream signaling molecules (*i.e.*, MyD88 and IKKβ) results in reduced tumor burdens[86,151,156]. A TLR4-dependent hyperproliferation of colonic epithelial cells was shown to be related to increased activation of COX/PGE2 and EGFR signaling in the mouse models of colon cancer[49,151,157].

Recently, we demonstrated that the abnormally upregulated TLR4 protein plays an anti-apoptotic role against its co-receptor CD14 during the development of colon cancer[158]. Stimulation with LPS induced CD14-mediated lipid signaling and led to colonic epithelial cell apoptosis, whereas TLR4 antagonistically promoted cell survival and cancer progression[29,158]. Our results showed that that dysfunction of this CD14/TLR4 antagonism in the context of the cellular death and survival response may contribute to the carcinogenic transformation of normal epithelial cells[158]. Finally, intracolonic administration of a TLR4 antagonist was shown to result in increased cancer cell apoptosis and reduced tumor burdern, suggesting the therapeutic potential of TLR4 blockade[158].

CONCLUSION

Greater understanding of the pathophysiological anti-death mechanisms that are present in cancer cells would enable advanced therapeutic interventions that could overcome chemoresistance. One of the key challenges of successful clinical translation is the ability to destroy tumors while sparing normal cells. By understanding the similarity between epithelial cytoprotection and cancer resistance, we may identify pathways that differ in normal and tumor cells for pharmacological manipulation. So far, abnormally expressed glucose transporters and TLR4, which are involved in both anti-death and pro-proliferative mechanisms, show great therapeutic potential. Drugs that target apoptotic machinery and signaling pathways, metabolic enzymes, and glucose transport are currently being investigated in clinical trials[159]. Agents to eliminate cancer stem cells, the cell type most resistant to death, are also in development[160]. In sum, targeting death resistance pathways may offer a promising therapeutic approach in addition to strategies such as inhibiting proliferation and angiogenesis and would offer hope to patients with refractory tumors.

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