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TOPIC HIGHLIGHT

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Targeting cell death signaling in colorectal cancer: Current strategies and future perspectives

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Abstract

The evasion from controlled cell death induction has been considered as one of the hallmarks of cancer cells. Defects in cell death signaling are a fundamental phenomenon in colorectal cancer. Nearly any non-invasive cancer treatment finally aims to induce cell death. However, apoptosis resistance is the major cause for insufficient therapeutic success and disease relapse in gastrointestinal oncology. Various compounds have been developed and evaluated with the aim to meet with this obstacle by triggering cell death in cancer cells. The aim of this review is to illustrate current approaches and future directions in targeting cell death signaling in colorectal cancer. The complex signaling network of apoptosis will be demonstrated and the "druggability" of targets will be identified. In detail, proteins regulating mitochondrial cell death in colorectal cancer, such as Bcl-2 and survivin, will be discussed with respect to potential therapeutic exploitation. Death receptor signaling and targeting in colorectal cancer will be outlined. Encouraging clinical trials including cell death based targeted therapies for colorectal cancer are under way and will be demonstrated. Our conceptual understanding of cell death in cancer is rapidly emerging and new types of controlled cellular death have been identified. To meet this progress in cell death research, the implication of autophagy and necroptosis for colorectal carcinogenesis and therapeutic approaches will also be depicted. The main focus of this topic highlight will be on the revelation of the complex cell death concepts in colorectal cancer and the bridging from basic research to clinical use.

Key words: Colorectal cancer; Apoptosis; Necroptosis; Autophagy; Clinical trial; Bcl-2 proteins; BH-3 mimetics; Inflammatory bowel disease

Core tip: This review highlights current strategies targeting cell death signaling in colorectal cancer. The role of apoptosis, autophagy and necroptosis in the normal colon mucosa as well as in colorectal cancer onset and therapy is defined. Relevant small molecule compounds as well as antisense based approaches for the treatment of colorectal cancer are illustrated. Furthermore, clinical trials investigating new cell death based compounds are discussed. Finally, future directions in translational cell death research are discussed.

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CELL DEATH IN THE NORMAL COLORECTUM

The crypts of the colorectal mucosa are organized in a

polarized fashion. Very few stem cells at the base of a crypt comprise the pool of the regenerative epithelium in which cells travel from bottom to top of the crypt. On the apical edge of the mucosa, about 10^{10} cells per day die by apoptosis and are subsequently shed in the lumen[1]. This fact illustrates the essential need of a proper regulated cell death for the homeostasis of a normal colorectal mucosa. However, defective signaling or dysbalanced regulation of apoptosis is a very likely cause for the initiation and progression of an adenoma to carcinoma sequence ending up in colorectal cancer (CRC). Of note, proteins relevant for apoptosis (*e.g.*, Bak or Bcl-2) are not equally expressed in all parts of the colorectal mucosa pointing on distinct regulation of death in the intestine[2,3].

In addition to apoptosis as the classical form of programmed cell death, autophagy, a controlled process of cellular self digestion of great importance in situations of cellular stress or upon energy deprivation, has been shown to be active and relevant in colorectal glands. In contrast to apoptosis, the autophagic flux intensity decreases in the crypt from bottom to top[4]. This has been indicated by high expression levels of proautophagic protein Beclin-1 and the conversion of LC3- I to LC3- II in lower crypt cells. On their way to the apex of a crypt the epithelial cells lose Beclin-1 expression and accumulate high levels of SQSTM1/p62, which is an ubiquitin-associated adaptor protein maintaining autophagic flux[4].

In summary, the integrity of the complex interplay of cell death signaling is fundamental for mucosal development and homeostasis in the colorectum. Defective or dysbalanced cell death signaling is involved in the pathogenesis of a variety of colorectal diseases from chronic bowel diseases (Crohn's disease as well as ulcerative colitis) to colorectal carcinoma.

CELL DEATH IN INTESTINAL DISEASE AND CARCINOGENESIS

Colorectal carcinoma can occur sporadically, the most common situation, on the base of defined mutations and also as a final consequence of chronic inflammatory diseases of the intestine[5,6]. The intriguing field of cancer related to chronic inflammation will not be in the focus of this review and the reader might refer to comprehensive literature by others addressing this issue[7-11].

During the development of CRCs from benign polyps through adenomas and finally adenocarcinomas, cell death plays a fundamental role. Key regulating proteins of an appropriate mucosal cell death undergo changes in expression during the transition of an adenoma-carcinoma-sequence[12-14]. For instance, antiapoptogenic Bcl-2 gets lost during the development from adenoma to carcinoma[14]. However, especially the value of cell death related proteins as biomarkers for prognosis and prediction of CRC is of great interest, but the available literature is inconsistent and controversial[15-17]. In summary, apoptosis signaling proteins are in the context of biomarkers either ill defined or need further validation[18]. The reason for these contradictory reports might be due to the extraordinary heterogeneity of CRCs and the broad variety of the carcinogenesis driving mutations[5,19,20]. The aim of this review is to identify possible targets in the cell death signaling network and discuss the compounds available to foster killing of colorectal cancer cells.

TARGETING CELL DEATH IN COLORECTAL CANCER

Apoptosis: Implications for therapy

Defects in apoptosis signaling are common in colorectal cancers. An acquired resistance towards cell death may be a key feature of both, carcinogenesis and therapy resistance[21]. However, proteins within the apoptosis signaling pathways have been evaluated for their value as predictive and or prognostic markers as well as targets for therapeutic approaches[18]. Figure 1 shows a synopsis of apoptosis signaling and indicates relevant targets and compounds.

INTRINSIC PATHWAY

Mitochondria are in the very centre of the intrinsic pathway of apoptosis. The mitochondrial membrane integrity is regulated by the Bcl-2 family of proteins. A tight balance of pro- and antiapoptotic Bcl-2 proteins governs cell's fate at the mitochondrial surface. In response to several unfavorable conditions (*e.g.*, growth factor withdrawal, DNA damage), this balance shifts towards death. In this case, the proapoptotic proteins (*e.g.*, BAX and BAK) are released by their antiapoptotic relatives (Bcl-2, Bcl-xL, Mcl-1, Bcl-w and A1)[22]. The proapoptotic proteins finally lead to mitochondrial outer membrane permeabilisation and the immediate release of cytochrome C (cytC) into the cytosol. Together with APAF-1 and Caspase 9, cytC forms a death inducing protein platform called apoptosome which in turn leads to activation of caspase 3 as the central downstream event of cell death execution[23].

BH3-mimetics

Within the intrinsic pathway of apoptosis, the antiapoptotic Bcl-2 proteins have been extensively studied as "druggable" targets. Various small molecules targeting the antiapoptotic proteins by binding to their BH3 cleft. This mechanism of action causes a release of multidomain proapoptotic Bcl-2 proteins (*e.g.*, Bim, Bak or/and Bax) which in turn promote cell death. ABT-737 and its orally available derivate ABT-263 (navitoclax) are potent inhibitors of Bcl-2, Bcl-w and Bcl-xL. ABT-263 has recently been shown to induce cell death in colorectal cancer cells *in vitro* synergistically with the inhibition of the prosurvival kinase MAP kinase/ERK kinase 1/2[24]. This mechanism of death induction by ABT-263 was completely dependent on Bax and Bim. Several phase I trials in solid cancers have proven the safety of ABT263 in combination with established therapy regimes (www.clinicaltrials.gov). ABT-737 has been shown to act synergistically with

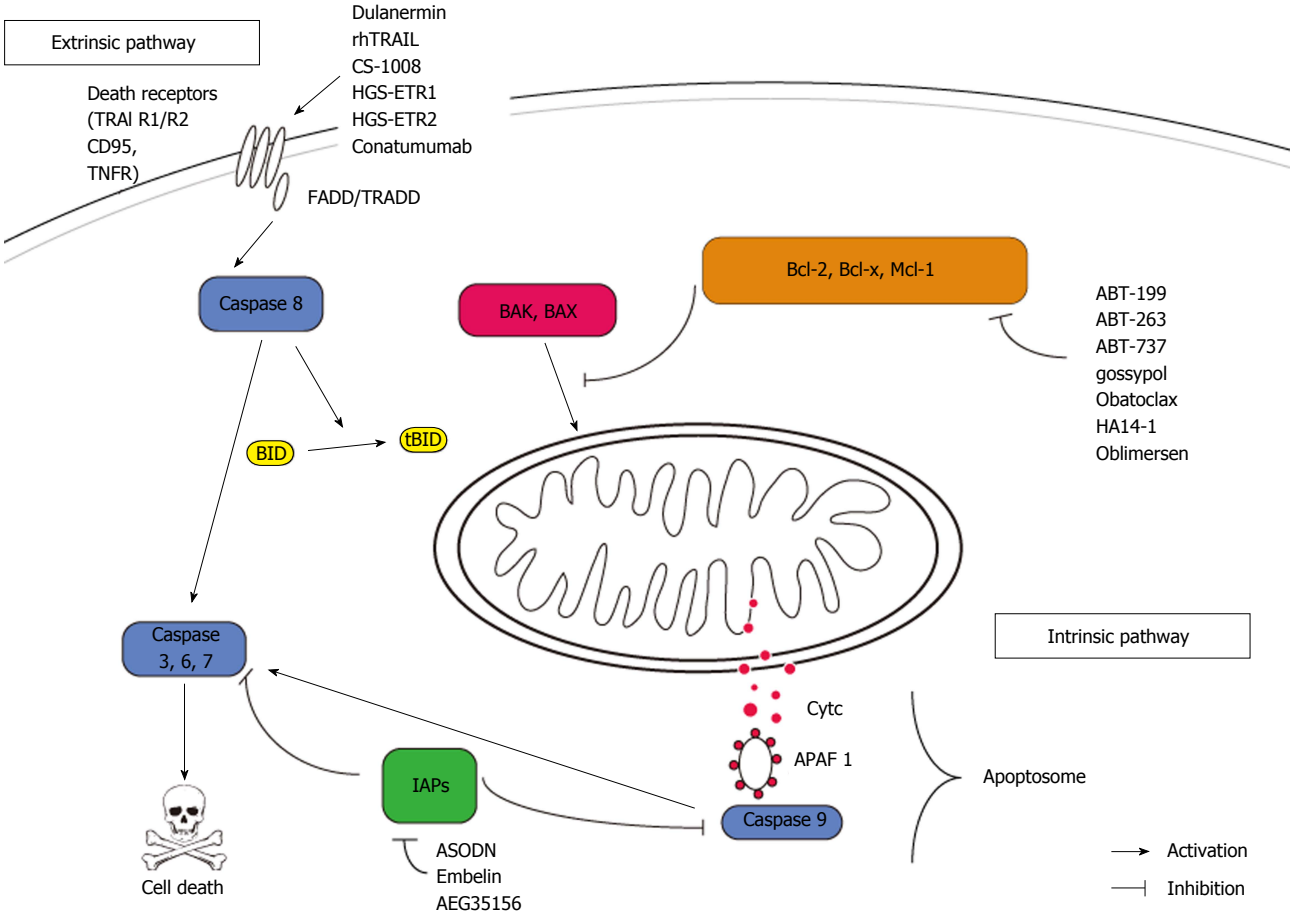

Figure 1 Apoptosis signaling and cell death relevant drugs. Cell death based cancer therapy can be approached by targeting proteins in the extrinsic or intrinsic pathway. Relevant agents, currently under clinical investigation, are listed and placed to their targets. APAF1: Apoptotic protease activating factor-1; CytC: Cytochrome C; IAP: Inhibitors of apoptosis; tBID: Truncated BID; FADD: Fas-associated protein with death domain; TNF: Tumor necrosis factor; TRAIL: Tumor necrosis factor related apoptosis-inducing ligand.

oxaliplatin on CRC cells *in vitro*[25]. An *ex vivo* evaluation of ABT-737 in samples of ovarian tumors is under way (www.clinicaltrials.gov). In addition, ABT-737 enhanced apoptosis in CRC cells induced by cyclo-oxygenase-2 inhibitor celecoxib[26]. Importantly, the sensitivity of cancer cells towards ABT-737 is dictated by the expression of NOXA and its control by Mcl-1, which is not targeted by ABT-737[27,28]. Interestingly, Mcl-1 sparing BH-3 mimetics such as ABT-737, ABT-199 and ABT-263, have been shown to effectively induce apoptosis in hypoxic regions of human colorectal tumor spheres. Hypoxia led to a profound downregulation of Mcl-1 which is responsible for ABT-737 resistance in many settings[29]. This work is of great interest since few normal tissues are exposed to hypoxia, but it is a common challenge for growing tumors[30]. HA14-1 is a highly selective small molecule targeting Bcl-2 only. HA 14-1 has been shown to overcome TRAIL resistance in CRC cells by counteracting Bcl-2 overexpression[31,32].

Obatoclax is a first-in-class BH-3 mimetic with an inhibitory profile including Bcl-2, Bcl-xL, Bcl-w, Mcl-1 and A1 (pan-Bcl-2-inhibitor)[33]. Given the crucial role of Mcl-1 for resistance towards BH-3 mimetics, obatoclax is a promising new agent targeting the complete antiapoptoic Bcl-2 protein family members at once. Few studies investigated the potency of obatoclax for colorectal cancer treatment. It has been recently shown that cell death induction through inhibition of the proproliferative protein Notch by gamma secretase inhibitors is fostered by obatoclax[34].

Oblimersen is an antisense oligonucleotide targeting the first six codons of Bcl-2. Antisense technology represents a highly specific approach for downregulation of antiapoptotic proteins without off-target effects[35]. A phase I trial has shown the safety of oblimersen in combination with irinotecan when intravenously administered in patients with metastatic CRC[36].

In summary, Bcl-2 proteins are context-sensitive targets in colorectal cancer treatment alongside established chemotherapy or radiation. Future studies are urgently warranted to reveal the potential of BH-3 mimetics in colorectal cancer in the clinical setting.

IAP inhibitors

The inhibitor of apoptosis (IAP) family acts by blocking caspase activity (primarily caspase 3). IAPs are found to be overexpressed in several cancer entities including CRC and are able to protect cancer cells from various death

stimuli[37,38]. Several compounds inhibit IAPs (primarily XIAP and Survivin). AEG35156 is a second generation antisense oligonucleotide targeting XIAP. Preclinical and early clinical data revealed a promising death-inducing potential of AEG35156 in several solid tumor entities including CRC[39-42]. Survivin is a second promising target among the IAP family overexpressed in CRC. Survivin antisense oligonucleotides strikingly cleared the way for death induction in CRC cells *in vitro*[43]. Embelin, a naturally occurring benoquinone, has been proven effective in various tumor entities by targeting survivin and other antiapoptotic proteins (Bcl-2 and Bcl-xL)[44]. In the colon, Embelin was able to sufficiently attenuate colitis and carcinoma development in rodents[45,46]. Finally, a double edged approach targeting survivin and XIAP might be a very promising approach for CRC treatment[47].

SMAC mimetics

Second mitochondria activator of caspases (SMAC)/Diablo is a mitochondria derived, proapoptotic protein acting by blocking IAPs thereby promoting caspase dependent cell death[48]. SMAC mimetics have been shown to strongly sensitize CRC cells towards NSAID induced apoptosis through a feedback amplification resulting in the activation of caspase 3[49]. In TRAIL-induced apoptosis in CRC cells, SMAC/Diablo release from the mitochondria plays a pivotal and role and is Bax dependent[50,51]. Further studies are warranted to clarify the exact role of SMAC for colon carcinogenesis and CRC therapy.

EXTRINSIC PATHWAY

The extrinsic pathway of apoptosis becomes activated in case of binding of a specific ligand to its surface death receptor. Most engaged receptors belong to the tumor necrosis factor receptor family (TNFR, CD95/FAS, TRAIL) and share broad similarity in structure and action[52,53].

In response to ligand binding, the receptor homotrimerises and an adaptor molecule (FADD, TRADD) containing a death domain (DD) is recruited to the cytosolic DD of the receptor. Procaspase 8 is hereafter recruited and catalytically activated in its active form. Finally, caspase 8 leads to an activation of caspase 3 where extrinsic and intrinsic pathways of apoptosis converge[54]. In addition to this direct road to death *via* caspase 8 and caspase 3, there is a possible detour integrating mitochondria to enhance the death signal. The BH3 only protein Bid is a direct target of Caspase 8 and after cleavage of Bid truncated Bid (tBid) is able to activate mitochondria herewith involving intrinsic apoptosis[55,56].

The receptors involved in extrinsic cell death signaling have been shown to be promising targets. Various compounds and approaches aim to induce apoptosis *via* direct receptor activation.

Tumor necrosis factor-α/tumor necrosis factor receptor

Recombinant tumor necrosis factor-α (TNF-α) has been approved for regional treatment of melanoma and soft tissue sarcoma in Europe. The use of TNF-α as a systemic approach is hampered by severe toxicity and adverse side effects such as hypotension, organ failure and cachexia[57]. The efficacy of TNF-α for CRC treatment remains to be clarified, but might be restricted due to TNF-α's nature as a proinflammatory cytokine. TNFerade® is an adenoviral delivered, intratumoral therapy with a proven safety in rectal cancer patients[58,59]. In advanced pancreatic cancer, TNFerade® was safe but did not prolong survival of patients[60]. The final investigation of TNFerade® for CRC treatment remains elusive. Furthermore, human monoclonal antibody-cytokine fusion protein L19-TNF has been shown to be safe in solid tumors and effective in sarcomas[61,62]. Again, more studies addressing the efficacy for CRC treatment are needed.

CD95 (Apo1/Fas)

CD95 and its ligand have a highly complex role in the colorectal mucosa as well as in onset and progression of CRC. In CRC tissue, CD95 has been shown to be expressed at higher levels compared to adjacent healthy mucosa[63]. Tumor stromal cells and infiltrating immune cells should be considered as bystander targets of CD95 triggering[64,65]. There is some evidence for a metastasis promoting function of CD95 signaling in colorectal cancer *via* induction of epithelial to mesenchymal transition[66]. As response to hypoxia and radiation, CD95 becomes activated on CRC cells and induces local invasion and promotes liver metastasis in mice[67,68]. In addition, invasive properties of CRC cells have been linked to CD95 signaling[69,70]. At least *in vitro*, CD95 participates in the activity of PEG-liposomal oxaliplatin induced death in CRC[71]. The anti-Fas monoclonal antibody CH-11 showed antitumor activity in CRC cells with high expression levels of CD95. This death inducing effect was effectively prevented by overexpression of Bcl-2 pointing on a pivotal role of mitochondria for CD95 signaling in CRC[72]. Moreover, there is evidence for a regulatory effect of other antitumor drugs [5-fluorouracil (5-FU), mitomycin (MM), cisplatin (CP) and all-trans retinoic acid] on CD95 expression of CRC cells. Here, MM and CP were able to increase CD95-induced apoptosis. By contrast, 5-FU led to a receptor downregulation causing immune escape of CRC cells[73]. In summary, CD95's value as a therapeutic target in CRC is complex and might be limited due to the multifaceted role of CD95 in immune-mediated tumor surveillance[74]. As for TRAIL detailed below, several ways of resistance to CD95-induced death further complicate CD95-based therapeutic approaches[75-77].

Tumor necrosis factor inducing ligand-system

Tumor Necrosis factor inducing ligand (TRAIL) receptors have been considered as extraordinary promising antitumor targets, since activation preferably kills tumor cells while sparing healthy cells[54]. However, normal colon mucosa epithelium is resistant to TRAIL-induced death[78]. TRAIL directly targets death receptor 4 (DR4)

Table 1 Targeting apoptosis in colorectal cancer: An overview of current clinical trials

Drug	Target	Clinical[1]	Ref.
Smac mimetics	IAPs	Phase I (NCT01573780)	[49,139]
Survivin peptide vaccine	survivin	Phase I - II (NCT00108875)	[140,141]
Oblimersen	Bcl-2	Phase I (NCT00004870)	[142,143]
Dulanermin	DR4/5 dual	Phase I b (NCT00671372)	[86]
Tigatuzumab	DR5	Phase I	[144]
CS-1008	DR5	Phase I (NCT01220999)	[145]
HGS-ETR1	DR4	Preclinical *in vivo*	[79]
HGS-ETR2	DR5	Phase I (NCT00428272)	[79,146]
rhApo2L/TRAIL	DR4/DR 5	Phase I - II (NCT00819169)	[147]
Conatumumab	DR5	Phase II (NCT01327612)	[148]
ABT-263	Bcl-2/Bcl-xl	Phase I (NCT00891605, NCT01009073)	[24]
ABT-737	Bcl-2/Bcl-xl	Preclinical *in vivo*	[25,26,30]
Gossypol	Pan-Bcl2	Preclinical *in vivo*	[149]

[1]Further detailed information on clinical trials: www.clinicaltrials.gov. The compounds included in the table directly target apoptotic proteins and show antitumor effects *in vivo*. The phase of the clinical trials is stated and trial identifier indicated in brackets where applicable. IAP: Inhibitors of apoptosis; DR: Death receptor; TRAIL: Tumor necrosis factor related apoptosis-inducing ligand.

and death receptor 5 (DR5). The recombinant, soluble ligand rhApo2L/TRAIL as well as several antibodies targeting DR4 and/or DR5 have been developed and tested for clinical use.

The agonistic DR4 antibody HGSETR1 (Mapatumumab) and the agonistic DR5 antibody HGSETR2 (Lexatumumab) induced apoptosis *in vitro* as well as in xenograft bearing nude mice when combined with radiation[79]. In addition, both agonistic antibodies have strong synergistic effects with the mitosis disrupting agent paclitaxel in CRC cells *in vitro* and *in vivo*. This sensitizing effect is due to an upregulation of the cognate receptors[80]. Several other antibodies targeting DR4 or DR5 have been shown to have strong antitumor potential on CRC cells[81-85]. Dulanermin (rhApo2L/TRAIL), an optimized and soluble form of TRAIL, has been successfully evaluated in early clinical trials[86]. A clinical trial with Dulanermin in combination with a chemotherapy backbone (FOLFIRI) for patients with metastatic CRC has been completed recently and data from this trial should be available soon (www.clinicaltrials.gov).

It is important to have in mind that several CRC cells show intrinsic or acquired resistance towards TRAIL-induced apoptosis. Several proteins have been shown to counteract TRAIL-induced apoptosis. For instance, two decoy receptors within the TRAIL system can counteract DR4 and DR5 activation[87]. Moreover, the interference of antiapoptotic Bcl-2 proteins with TRAIL-receptor-mediated apoptosis has been reported[54,88]. Again at the mitochondrial level, Bax is apparently mandatory for TRAIL's efficiency to kill CRC cells, since Bax deficiency completely abrogates TRAIL-induced death[89]. Furthermore, high levels of XIAP block TRAIL-induced mitochondrial activation[90]. At the receptor level, mutations of caspase 8 have been reported to cause TRAIL resistance[91]. Moreover, high expression levels of FLIP counteract the interaction between the adaptor FADD and Caspase 8 in CRC cells[92,93]. Pennarun and coworkers presented proof of concept of a combined approach: Downregulation of Mcl-1 and FLIP by multikinase inhibitor sorafenib and NSAID aspirin resensitized cells towards TRAIL[94]. These data are indicative for the feasibility of a combination approach of TRAIL receptor targeting and mitochondrial activation, *e.g.*, by BH3-mimetics.

Taken together, a final and clinical proof of concept for individualized TRAIL tailored therapy for CRC is still elusive and large cohort prospective trials addressing this issue are needed. Table 1 provides an overview of strategies and trials targeting TRAIL receptors in CRC. The awaited results from the Dulanermin trial in metastatic CRC might gain important information for further study designs using TRAIL based therapy.

ALTERNATIVE CONTROLLED CELL DEATH IN COLORECTAL CARCINOMA

The conceptual understanding of cell death is under constant expansion and various subtypes of cellular death have been defined[1,95,96]. Among the emerging cell death concepts, this work will deeper discuss necroptosis and autophagy in order to dissect the current knowledge concerning colorectal carcinogenesis and CRC treatment.

Necroptosis

Necrosis has long been considered as a passive, mainly accidental and uncontrolled form of cellular death. To date there is a growing body of literature implicating a tight regulation of necrotic processes similar to apoptosis[97]. Therefore, a programmed form of necrosis, termed necroptosis, has been defined. The signaling events responsible for initiation and execution of necroptosis have been studied best in the context of TNFR signaling. Necroptosis is crucially mediated by receptor-interacting protein 1 (RIP 1) along with its cognate kinase RIP3. Upon TNF induction, a multimeric complex containing FADD, caspase 3, RIP 1 and RIP 3 assembles[98]. This complex is termed complex IIb or necrosome. The determination of cells' fate is complicated by the observation that the ubiquitination status of the engaged proteins (*e.g.*, RIP) appears to be the master switch between apoptosis and necroptosis[99]. Necroptosis has also been demonstrated after activation of TRAIL receptors on hepatocytes and colorectal cancer cells[100]. Mechanistically, there are various central proteins involved in both, apoptosis and necroptosis. Which form of cell death prevails, is cell type and stimulus dependent[101-103]. Necroptosis and its role in various diseases, including CRC and inflammatory bowel disease, are currently under investigation[104-107]. There is evidence for a central role of caspase 8 as a key switch from apoptosis to necroptosis in carcinoma re-

Table 2 Targeting autophagy in colorectal cancer: An overview of current clinical trials

Drug	Target	Clinical[1]	Ref.
Hydroxychloroquine	Autophagosome	Phase I (NCT01206530) Phase II (NCT01006369)	[122,150]
Everolimus/rapamycin	mTOR	Phase II (NCT00419159, NCT01387880)	[126,127,151]

[1]Further detailed information on clinical trials: www.clinicaltrials.gov. The compounds shown target relevant processes or proteins involved in autophagy signaling. The phase of clinical trials is stated and trial identifier indicated in brackets where applicable. mTOR: Mammalian target of rapamycin.

lated inflammatory bowel disease[104].

The relevance of necroptotic cell death for colorectal cancer cells has been evaluated preclinically in the context of azathioprine plus buthionine sulfoximine treatment in CRC and HCC[108]. This work shows a necroptosis phenotype with mitochondrial dependency illustrating the interplay between necroptosis and apoptosis. Another study investigated the role of hypoxia for necroptotic death in colorectal cancer cells. In this study, RIP-dependent necroptosis can be conferred by pyruvate scavenging of mitochondria derived radicals[109]. Finally, targeted approaches to induce necroptotic cell death in cancer cells are still missing due to the absence of appropriate compounds for clinical usage so far. It has been shown that TRAIL receptor ligation causes necroptosis in an acidic extracellular milieu. Necrostatin-1, a chemical inhibitor of RIPK1, sufficiently blocked TRAIL-induced necroptosis in this experimental setting[100]. An indirect or secondary activation of necroptosis has been reported after treatment of CRC cells with TRAIL or inhibition of the multifaceted kinase GSK3-β[100,110].

Autophagy

Autophagy is an evolutionary conserved process by which cells collect proteins and organelles, deliver them to the lysosomal compartment where the cargo is finally degraded for recycling[111]. The implications of autophagy for cell physiology as well as for onset and progression of various diseases including cancer are rapidly emerging[112,113]. A disruption of autophagic flux leads to an intracellular accumulation of organelles, protein aggregates and lipid droplets. These accumulations may lead to the production of reactive oxygen species and cause metabolic insufficiency. Especially in stressful situation and in conditions of energy deprivation, a disruption of autophagic flux can promote carcinogenesis. For instance, the allelic loss of the essential autophagy protein Beclin 1 (also known as Atg6) causes HCC in mice[114,115].

By contrast, autophagy is essential for the survival of cancer cells and cancer cells show an extraordinary high level of autophagy. However, autophagy induction promotes survival under conditions of hypoxia and growth factor withdrawal[116]. Autophagosome formation is most prominent in tumors growing in a hypoxic environment. With regard to these findings, drugs inhibiting autophagy are promising anticancer agents. The anti-malaria drug Chloroquine is a known inhibitor of autophagy and is currently being under investigation in several clinical trials (www.clinicaltrials.gov, Table 2)[117]. Various other compounds or drugs are known regulators of autophagy and have been evaluated preclinically as treatment options for CRC[118-121]. *In vitro*, Chloroquine has been effective in overcoming 5-FU resistance in CRC cells[122,123]. Intriguingly, the approved chimeric anti-EGFR antibody cetuximab exerts its antitumor effect at least partly *via* autophagy-induced cell death[123].

Counterintuitive, drugs directly inducing autophagy are under clinical investigation as therapeutic approaches in CRC, too. Mammalian target of rapamycin is a prominent target to induce lethal autophagy in colorectal cancer cells[124]. The Rapamycin derivate Everolimus has recently been established for the treatment of colorectal neuroendocrine tumors[125]. A Phase II study with Everolimus showed appropriate tolerability, but failed to show meaningful efficacy in heavily pretreated patients with metastatic CRC[126]. Another trial using a combination of vascular endothelial growth factor receptor tyrosine kinase inhibitor tivozanib with everolimus resulted in stable disease of 50 % of all patients with metastatic cancer enrolled[127,128]. These partly contradictory findings highlight the important implication of autophagy in colorectal carcinogenesis.

Importantly, there is a broad overlap of the apoptosis and autophagy signaling network. Most prominently, Bcl-2 proteins function as both, inhibitors of apoptosis and autophagy by binding proautophagic Beclin1. Therefore, it has been shown that BH3-mimetics induce apoptosis and autophagy. For instance, ABT-737 can synergistically induce cell death with the COX2 inhibitor celecoxib in CRC cells by facilitating autophagy and apoptosis[26,129].

CROSSTALK BETWEEN APOPTOSIS, NECROSIS AND AUTOPHAGY: MULTI-DEATH TARGETING STRATEGIES

The past decade of cell death research has shown that necrosis, apoptosis and autophagy are regulated by similar pathways engaging the same proteins. It might be worthwhile targeting the apoptotic and autophagic machinery in a combined approach, since a massive induction of autophagy is able to drive cancer cells in apoptotic death. Recently, various efforts in this direction have been made in order to overcome cell death resistance in colorectal cancer. For instance, silibin, a plant derived

natural compound, is able to induce both, apoptosis and autophagy[130]. In line with these observations, compound C, a small molecule inhibitor of AMP-activated protein kinase, is able to sufficiently suppress colorectal cancer cell growth by inducing apoptosis and autophagy[131]. The capability of such a double-edged approach has been successfully proven *in vivo* in a model of hepatic metastasis in mice[132]. Future studies are needed to further exploit combinatorial approaches for cell death induction in colorectal cancer.

CONCLUSION

From an oncological point of view, it is of outstanding importance to further increase research efforts aiming at more effective and individualized therapies. The effectiveness of monotherapeutic systemic approaches in colorectal cancer treatment is limited. However, combined therapy regimes are now state of the art. Manipulation of cell death represents a promising tool to further amplify response to chemotherapy. In addition to direct cell death induction in cancer cells, triggering cell death *via* cancer-directed immunotherapy or immunomodulation with the aim to overcome major mechanisms of immune resistance, is a newly arising field[133]. For example, recent reports on long-term results from first-in-human clinical trials using anti-PD1 antibody-based immunotherapy are encouraging[134]. Future trials are warranted to identify the best combinatorial approach yielding at cell death induction in cancer cells.

On the way to personalized oncology, it will be mandatory to broaden our knowledge concerning the selection of patients for a specific therapeutic setting. Having in mind that cell death relevant proteins vary in their expression in different subsets and stages of CRC, a stratification of patients to identify those who benefit most of a manipulation of apoptosis requires further research.

Finally, the question whether and how cell death could be measured to monitor therapy in patients needs further attention. There are some elegant and encouraging studies evaluating liquid biopsy markers for cell death in cancer[135,136]. In addition, imaging of cell death on routine basis for non-invasive monitoring of tumor biology and therapeutic response might open new windows for therapy surveillance and outcome prediction in colorectal cancer[137,138].

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