

Mini Review

(RIP1)/RIP3-Regulated Necroptosis, Interplay with Apoptosis and Autophagy, and Its Therapeutic Effect on Leukemia

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Abstract

Apoptosis resistance is a major obstacle leading to chemotherapy failure during cancer treatment. Necroptosis is an alternative mode of programmed cell death with necrotic morphology, mediated by signal transduction from Receptor-Interacting serine/threonine kinase (RIP1) to RIP3 and its modality is the caspase-independent pathway. Necroptosis cell death overcomes apoptosis resistance and amplifies antitumor immunity in cancer therapy. The role of necroptosis in leukemia is unknown. This mini review aims to provide a better understanding of necroptotic pathway mechanisms, their interaction with other forms of cell death, and the implications of necroptosis and RIP-1/RIP-3 on leukemia treatment. First, a brief introduction of the types of cell death is given. The interplay between necroptosis and other cell death mechanisms in leukemia is then explained and a summary of the effects of necroptosis on leukemia therapeutics is provided.

Keywords: Apoptosis; Autophagy; Necroptosis, Leukemia, Receptor-interacting serine/threonine kinase (RIP1) to RIP3

Abbreviations

ALL: Acute Lymphoblastic Leukemia

AML: Acute Myeloid Leukemia

FADD: Fas-Associated protein with Death Domain

HDAC: Histone Deacetylase

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Nec- 1: Necrostatin-1

NF- κ B: Nuclear Factor kappaB

RIP1/RIP3: Receptor-interacting serine/ threonine-protein

Smac: Second mitochondria-derived activator of caspases

TNF: Tumor Necrosis Factor

TNFR: TNF Receptor

Bcl-2: B cell lymphoma-2

BH-3: Bcl-2-Homology

Cyt c: Cytochrome c

DD: Death Domain

IAP: Inhibitor of Apoptosis Protein

JNK: Jun N-terminal Kinase;

LC3: Microtubule-associated protein 1A/1B-light chain 3

TRADD: TNF Receptor-Associated Death Domain

VDAC: Voltage-Dependent Anion Channel

MAPK: Mitogen-Activated Protein Kinases

PI3K: Phosphatidy Inositol 3-Kinase;

PE: Phosphatidyl Ethanolamine

SMAC: Second Mitochondria derived Activator of Caspase

APAF- 1: Apoptosis Protease Activating Factor

MAC: Mitochondrial outer membrane

TRAIL: TNF-Related Apoptosis-Inducing Ligand

LC3-II: Phosphatidylethanolamine conjugate

RHIM: RIP1 Homotypic Interaction Motif

cIAPs: cellular Inhibitor of Apoptosis Protein

MLKL: Mediator Mixed-Lineage Kinase Domain like.

Introduction

Cell death is the stopping of a biological cell from functioning. This may be the result of a normal process in which old cells die and are replaced by new ones, or may be caused by other factors such as diseases, injury to a specific organ, or death of the organism itself and considerable importance in the cell's life cycle [1].

Dead cells can be identified based on morphological or molecular features that include loss of cell membrane integrity, fragmentation of cell organelles such as the nucleus, and phagocytosis of cell fragments [2]. Cell death can be categorized as autophagic, necrotic, and apoptotic, depending on the cell morphology (Figure 1) [2,3].

Programmed Cell Death (Apoptosis)

In a healthy adult human being, around 10 million cells die via apoptosis every day. Apoptosis is mostly described as programmed cell death since it is a phenomenon during which a cell sets off its own death i.e. suicide [4]. The degree of apoptotic death is important in maintaining homeostasis, as well as, in controlling the shape and size of tissues during various developmental processes. This programmed cell death is also essentially required to reduce the number of immune effector cells once the pathogen has been eliminated [5].

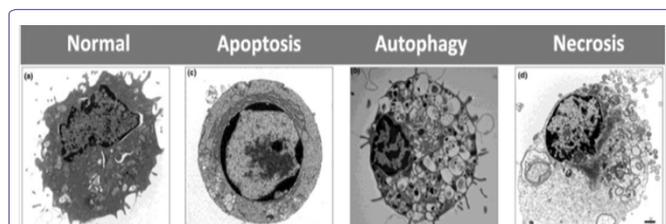


Figure 1: Shows the morphological features and differences between apoptosis, autophagy and necrosis versus normal cell. **a)** Normal cell; **b)** autophagic showing the massive formation of (double-membraned) autophagic vacuoles; **c)** apoptotic cell showing the typical round shape and chromatin condensation; **d)** necrotic cell showing increased cell size, rupture of cell membrane and vacuoles formation.

During apoptosis, a cell becomes round, and its volume is reduced. This process is called pyknosis. In addition, chromatin material becomes condensed and the nucleus becomes fragmented. This phenomenon is called karyorrhexis. Apoptosis is also accompanied by plasma membrane blebbing. However, there occur insignificant ultra-structural modifications of cellular organelles. Blebs serve as the progenitors of apoptotic bodies having small, almost round cytoplasmic fragments surrounded by cell membrane. Moreover, it is possible that apoptotic bodies contain functional organelles enclosed in unbroken cell membrane [6,7]. Apoptotic bodies express phosphatidylserine on their surface. It is a phospholipid attached to the cell membrane and it functions as an “eat me” signal in order to attract phagocytic cells such as macrophages, which phagocytose these bodies [1,6,7].

There are two main pathways to apoptosis, namely, the death receptor pathway (extrinsic pathway) and the intracellular stress signals pathway (intrinsic pathway) [8].

The extrinsic pathway is activated by signals such as toxins, hormone, growth factors, nitric oxide or cytokines. The signals come from outside the cell and transduce through the plasma membrane for apoptosis to occur. The intrinsic pathway initiates in response to glucocorticoid and signals such as heat, radiation, hypoxia, viral infection, or raised calcium level inside the cell [9].

Apoptosis extrinsic pathway (Death receptor pathway)

Tumour Necrosis Factor (TNF) is the cytokine generated from activated macrophages and initiates the apoptosis through the extrinsic pathway [9]. TNF combines with Tumour Necrosis Factor-Receptor (TNF-R) and subsequently activates caspase, a fundamental apoptotic protein. The intermediate membrane protein called TNF Receptor-Associated Death Domain (TRADD) and Fas-Associated Death Domain protein (FADD) signal to caspase for apoptosis [8].

Apoptosis intrinsic pathway

The transduction of intrinsic pathway inside the cell can increase permeability of mitochondrial outer membrane, thus, allowing mitochondrial proteins to escape and disperse into the cell cytosol [10].

Mitochondria are the most crucial organelles in the regulation of apoptosis. Cytochrome c (Cyt c) is the first protein released from mitochondria for apoptosis, through configurative channels on mitochondrial outer membrane (MAC). Cyt c binds to apoptosis protease activating factor (APAF-1) to form Cyt c/APAF-1 complex termed as apoptosome [11]. Cyt c/APAF-1 complex consequently binds to

pro-caspase-9; then apoptosome cleaves pro-caspase into active form with the purpose of activating caspase 3 [10].

Voltage Dependent Anion Channel (VDAC) is a mitochondrial outer membrane protein that can control apoptosis by regulating mitochondrial outer membrane pores permeability [9]. The second mitochondria derived activator of caspase (SMAC) is a regulatory protein released in the cell, as a result of an increase in mitochondrial permeability. It plays an important role in apoptosis, as it deactivates inhibitor of apoptosis protein (IAP) which represses caspase activity [7-9]. Smac/Diablo is the second apoptotic factor after Cyt c but with a different function. Cyt c is the direct trigger of APAF-1 and caspase-9 whereas Smac/Diablo antagonize Baculovirus Inhibitor Repeat (BIR - a domain of IAP) and facilitates activation of caspase indirectly [9].

Autophagy

About fifty years ago, researchers discovered the phenomenon of autophagy. However, substantial molecular information about this process has been obtained during the past 5-7 years. This information has given insight into the form and functions of this phenomenon [12,13]. It has now been established that autophagy is the major cellular catabolic mechanism that safeguard the cell from different stresses such as deficiency of growth factors, nutrients or hypoxia instigated stress. It plays a crucial role in recycling the cellular organelles, proteins and other components. Therefore, it ensures cleanup of the cell, as well as, the provision of new constituents to build up various parts of the cell [14]. Autophagy is an ubiquitous phenomenon that take place in all types of cells. However, deficiency of nutrients or other stresses can result in upregulation of this process [14]. Researchers have also determined an association between autophagy and etiology of a number of human diseases such as cancer, metabolic disorders and neurodegenerative disorders [15]

Autophagy is of substantial importance for humans, especially in protection from a number of disorders. Its role in causation and prevention of different disorders is now well established. Numerous myodegenerative and neurodegenerative disorders are described by an elevated, yet inadequate autophagic activity. This shows how important autophagy is for the quality control of proteins. Likewise, if protein damage, mitochondrial damage or DNA damage caused by cellular stress is not followed by appropriate autophagic repair pathways, the affected cells become susceptible to becoming cancerous cells [16]. As mentioned above, induction of autophagy occurs in response to different cellular stress conditions like nutrient deficiency. Autophagosomes which are intracellular organelles and proteins impounded by double membrane vesicles are delivered to lysosomes during this process, so that they can be degraded. A growing number of evidence indicates that autophagy acts as a membrane trafficking system which supplies the parts of cytoplasm to the lysosomes for degrading protein in bulk, thereby, ensuring not only the survival of the cells but also quality control of the protein content of the cell through the elimination of abnormal proteins. Even though autophagy is viewed as a pathway for ensuring survival of the cell, unnecessary autophagy can induce necroptosis i.e., the so called type II programmed cell death.

Mechanism of Autophagy

During the course of autophagy, an autophagosome is formed when phagophore closes after engulfing cytoplasmic constituents and

cellular organelles. Phagophore is a pre-autophagosomal structure having cup-like shape and is also known as isolation membrane [17]. The next step is normally a fusion of autophagosome with lysosomal vesicles, resulting in proteolytic breakdown of the engulfed substances through the action of lytic enzymes contained in the lysosomes [18].

A pair of ubiquitin-like modifications is needed for the preliminary development of the sequestering membrane. These include the formation of Atg12-Atg5 conjugation system and the Atg8-Phosphatidylethanolamine (PE) complex [19]. In Atg12-Atg5 conjugation system, a covalent bond binds the smaller Atg12 protein with the Atg5 [20]. Atg7 acts as E1 enzyme and activates the Atg12 first, followed by the development of thioester bond between the two proteins. Then, Atg12 gets linked to Atg10 which is E2-like enzyme, resulting in the formation of a new thioester bond. Finally, through its glycine at carboxyl end, the Atg12 protein gets attached to amino group in the lysine residue of Atg5 [20,21]; however, this bonding is irreversible. Through its coiled coil domain at carboxyl end, the Atg16 gets attached to the Atg12-Atg5 complex and this bigger complex forms temporary association with the isolation membrane or phagophore [19-21]. The second conjugation system needs this complex for its formation. However, the Atg12-Atg5 conjugate splits after the formation of autophagosome.

The Atg8/LC3-PE complex is the 2nd conjugation system and is the best-defined marker for autophagosomes. Cysteine proteinase Atg4 processes Atg8 by cleaving the arginine residues at the carboxyl end, thereby exposing a glycine residue. Atg7 activates this glycine followed by transference of Atg8, an E2-like enzyme, to Atg3 [20]. Eventually, the conjugation of Atg8 with phospholipids PE occurs, thus, permitting the binding of protein with the autophagosomal membrane. The Atg8-PE complex is dissociated by the same Atg4 enzyme, leading to the recycling of Atg8 back to the cytoplasm. The cytosolic LC3-I form is produced when an Atg4 cysteine proteinase i.e. autophagin cleaves the newly formed LC3. The LC3-I form, having molecular weight of 18kDa, undergoes few ubiquitination-like reactions, leading to the generation of the membrane bound protein LC3-II. This LC3-II protein (16kDa) binds to both the outer and the inner sides of the developing autophagosome [22].

Autophagy Signalling Pathway

Autophagy cascade kinases

Phosphatidylinositol 3-Kinase (PI3K) is one of the first kinases to be verified as involved in autophagy. There are three groups of PI3K in mammal's cells [23]. Among these groups, class III PI3K plays an important role in the autophagy mechanism. Class III PI3K activates autophagy. On the other hand, autophagy is negatively regulated by class I PI3K. It has also been established that class III PI3K demonstrates interaction with Beclin 1 and p150. Beclin 1 was actually isolated as Bcl-2 interacting protein. Moreover, it serves as the first autophagy related tumour suppressor gene [24].

Serine/threonine kinase Atg1 is the 2nd major kinase involved in the pathway of autophagy. It develops a complex through interaction with different regulatory proteins and under different nutrient conditions, leading to the formation of complexes with different compositions. Partial dephosphorylation of Atg13 occurs in starvation conditions, followed by development of autophagosome, through an

interaction between dephosphorylated Atg13 and Atg1. However, in nutrient-rich environment, phosphorylation of Atg13 occurs and its interaction with Atg1 is inhibited, thereby, leading to inactivation of autophagy. Moreover, under nutrient-deficient conditions, association between Atg17 i.e. another Atg protein, and the Atg1-Atg13 complex is augmented [25].

Autophagy proteins; Beclin 1

Beclin 1 is the first mammalian gene to be identified as having a role in mediating autophagy. Beclin 1 is a novel Bcl-2-homology (BH)-3 domain only protein. Anti-apoptotic Bcl-2 family members interact with the BH3 domain of Beclin 1 [26]. Beclin 1 is localized within the plasma-membrane, the cytoplasm and the nucleus in human and murine [27]. Transcriptionally, nuclear factor (NF)- κ B is involved in the regulation of Beclin 1 expression. NF- κ B directly binds the Beclin 1 promoter and upregulates its mRNA and protein levels, leading to positive modulation of autophagy in T cells [28].

Autophagy proteins; Microtubule-associated protein 1A/1B-light chain 3 (LC3)

All mammalian tissues and cultured cells possess microtubule-associated protein 1A/1B-light chain 3 (LC3), which is a soluble protein with a molecular weight of about 17 kDa. Various components of cytoplasm such as cellular organelles and proteins found in cytosol are engulfed by autophagosomes during the course of autophagy. At the same time, LC3-I i.e. a cytosolic form of LC3, conjugates with phosphatidylethanolamine, resulting in the formation of LC3-phosphatidylethanolamine conjugate (LC3-II). This conjugate is then recruited to autophagosomal membranes. Autolysosomes are formed by the fusion of autophagosomes and lysosomes. Hydrolase enzymes contained in the lysosomes degrade the intra-autophagosomal components. The degradation of LC3-II in the lumen of autolysosomes occurs simultaneously [29].

Programmed Cell Death II (Necroptosis)

Historically, cell death was believed to be either programmed, called "apoptosis", or passive, called "necrosis". Apoptosis was considered instrumental to development and other physiological functions, while necrosis was seen as a response to inflammation conditions. Now, necrosis is known to have programmed aspects, with "necroptosis" describing regulated necrotic cell death that bears a mechanistic features to apoptosis and morphological features to necrosis.

Apoptosis and necrosis are characterized by different mechanisms leading to cell death. Apoptosis is associated with nuclear disintegration, followed by removal of the cell by macrophages. In necrosis, the nucleus stays intact and instead the membrane becomes swelling, resulting in leakage of cellular components. Apoptosis mainly occurs during embryogenesis, while necrosis is more common during disease states. Necroptosis falls somewhere in the middle, with several molecules and processes that can trigger, modulate, and effect necroptosis in cells [30].

Kinnally et al., [31] and Smith and Yellon [32] have both proposed that there are two apoptotic pathways which are partially interlinked. These include the classical apoptosis which is dependent on caspase, and caspase-independent programmed cell death. Both of these mechanisms can be associated with each other, since caspases may cause the activation of non-caspase proteases and vice versa.

Apoptosis is promoted by death receptors through an intracellular motif termed Death Domain (DD), causing the activation of caspases-8 and thereby, inducing apoptosis. Once the caspase-8 is inhibited, activity of the Jun Amino-Terminal Kinase (JNK) and DD-containing kinase RIP-1 results in the induction of a type of cell death which leads to the production of autophagosome, and which is dependent on Atg6/Beclin 1 and Atg7 [26].

It has been recently determined that T lymphocytes, stimulated by mitogens, induce nonapoptotic active caspases-8. Moreover, T cells devoid of this caspases-8 activity can enter the cell cycle. Nevertheless, they are unable to accumulate and undergo caspase-independent cell death. It was determined that this cell death results from chemical inhibition of RIP-1 and the necroptotic inhibitor Nec-1 caused restoration of T cells increasing in number. A parallel study conducted by Chen and colleagues reported that knockdown of RIP-1, mediated by Nec-1, restores the ability of T cells lacking in caspase-8, to demonstrate clonal expansion. This implies that kinase activity of RIP-1 is important for this mechanism of cell death [33].

RIP1/RIP3 complex

The human RIP gene encodes seven splicing isoforms: RIP1, RIP2, RIP3, RIP4, RIP5, RIP6 and RIP7 [34]. The Receptor Interacting Protein 1 (RIP1) is essentially required for the induction of necrosis and it is identified to interact with death domain (DD) of receptor Fas (CD95) and trigger programmed death response in cells [35]. Moreover, RIP3 is a protein attenuating RIP1 and tumor necrosis factor receptor 1 (TNFR1) induces NK-kB activation [36] RIP1 and RIP3 are regulated by ubiquitination and caspases. NF-κB and Mitogen-Activated Protein Kinases (MAPK) are activated by ubiquitination of RIP1 to enhance cell survival [37]. On the other hand, caspase-8 triggers apoptosis pathway upon deubiquitination of RIP1 [37]. RIP1/RIP3 complex is formed when RIP1 combines with RIP3 via C-terminal death domain, the intermediary RIP-1 Homotypic Interaction Motif (RHIM) as a result of inhibition of caspase-8 [38]. Three different domains can be identified in RIP1. These are the C-terminal death domain, the intermediary RIP1 homotypic interaction motif (RHIM)-domain and the N-terminal kinase domain [39,40]. RIP1/RIP3 complex triggers necroptosis via downstream signal transduction [38].

Upon stimulation of TRAIL or TNF, necrosome is formed, and it in turn, activates RIP3. Upon activation, RIP3 interacts with enzymes regulating glycolytic flux, glutaminolysis, leading to the formation of reactive oxygen species in the mitochondria [39,40]. It has now been established that the activity of RIP1 is linked specifically with necrosis, instead of apoptosis. Moreover, necrostatin-1 (Nec-1), a small molecule which inhibits necroptosis, impedes the RIP1 kinase activity [41]. So far, researchers are unable to identify any substrate of RIP1 that could have a role in necroptosis [1].

A prototypic signaling pathway to necroptosis is engaged by the binding of TNFα to its cognate cell surface receptor TNF receptor 1 (TNFR1), which triggers formation of the so called complex I at the TNFR1 [42]. This leads to K63-linked polyubiquitination of RIP1 by cellular inhibitor Nuclear Factor kappaB (NF-κB). Upon internalization of TNFR1, secondary cell death complexes assemble in the cytosol. When caspase-8 activation is blocked, RIP1 is no longer cleaved and can interact with RIP3 to build up the necrosome resulting in activation of RIP1 and RIP3 in an autocrine/paracrine manner via

reciprocal phosphorylation [43]. RIP3 subsequently phosphorylates and activates MLKL, a pseudokinase that lacks intrinsic kinase activity [44]. Upon its activation, MLKL forms oligomers and translocates from the cytosol to the plasma and intracellular membranes, where it disrupts membrane integrity (Figure 2) [45,46].

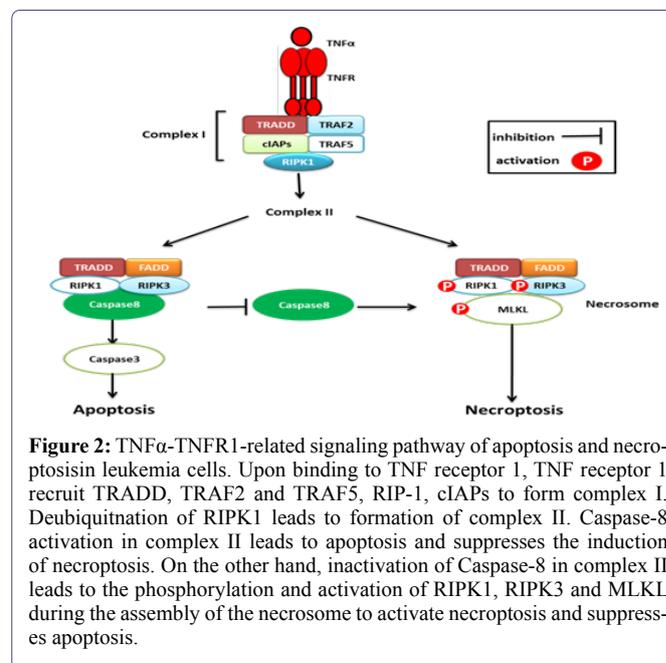


Figure 2: TNFα-TNFR1-related signaling pathway of apoptosis and necroptosis in leukemia cells. Upon binding to TNF receptor 1, TNF receptor 1 recruits TRADD, TRAF2 and TRAF5, RIP-1, cIAPs to form complex I. Deubiquitination of RIPK1 leads to formation of complex II. Caspase-8 activation in complex II leads to apoptosis and suppresses the induction of necroptosis. On the other hand, inactivation of Caspase-8 in complex II leads to the phosphorylation and activation of RIPK1, RIPK3 and MLKL during the assembly of the necrosome to activate necroptosis and suppresses apoptosis.

Necroptosis may offer an alternative option to trigger programmed cell death in cancer cells, as many cancers have evolved mechanisms to evade cell death [47]. In apoptosis-resistant cancers, therapeutic induction of necroptosis may be of particular interest, as activated caspase-8 has been shown to cleave and thus inactivate RIP1 [48]. This implies that apoptosis-resistant cancer cells are particularly susceptible to necroptosis.

Linking Autophagy and Apoptosis

There are two possible ways through which one can link the phenomena of autophagy and apoptosis. Firstly, the autophagy could demonstrate a regulatory role for apoptosis by increasing or decreasing its chances to occur. Secondly, apoptosis could demonstrate a regulatory role for autophagy by enhancing or reducing it [13]. Beclin 1 is an autophagic substance which is overexpressed under the influence of nutrient depletion, hypoxia, angiogenesis inhibitors, immunotherapy, irradiation, or chemotherapy [49]. Cancerous cells are protected from apoptosis through bid knockdown which also stimulates autophagy and this is manifested by enhanced expression of Beclin 1. However, the current literature is still deficient in elaborating the exact mechanism involved in inhibition of apoptosis by Beclin 1.

During apoptosis, Beclin 1 can be cleaved by caspases, resulting in the confiscation of its pro-autophagic action. Caspases are cysteine aspartyl proteases which play a crucial role in apoptosis and are stimulated by a death receptor ligand i.e., TRAIL [24,50]. Beclin 1 cleavage, mediated by caspase-3, -7 and -8, results in the formation of C- and N-terminal fragments, leading to loss of the ability to induce autophagy. The C-terminal fragments move to the

mitochondria and this make the cells sensitive to apoptotic signals [51]. Autophagy is decreased by apoptosis triggered by the proapoptotic protein Bax via increasing Beclin 1 cleavage at D149, mediated by caspase [52]. Nevertheless, it has been reported by some latest research studies that autophagy can result in degradation of a death receptor effector i.e. caspase-8, which implies that living systems have a feedback mechanism for cross-regulation of apoptosis and autophagy. Even though autophagy is inactivated by the apoptosis-related cleavage of Beclin 1 and Atg5, caspase-3-mediated Atg4D cleavage produces a fragment, capable of demonstrating enhanced autophagic activity [49].

Fundamental Necroptosis Mechanism in Leukaemia Treatment

Cell death is an essential cellular process thereby justifying the existence of more than one form of cell death processes. Principally, apoptotic pathways that cause cell death are of crucial significance throughout the organism growth and for regulation of the immune system while controlling defense response to a disease stimulus. Cell death is inter-connected with both cell- endurance and cell-expansion, through the control of molecular pathways [53]. It's evident that inter-connection and inter-dependence among death processes can give diverse outcomes.

Among various types of cell death; apoptosis and autophagy are the most interesting area for researchers. The induction of necroptosis has emerged in recent years as an alternative therapeutic approach to trigger programmed cell death in cancer cells, in particular in apoptosis-resistant cases [54].

It's crucial to investigate the role of necroptosis and RIP1/RIP3 in the combination with apoptosis and autophagy because its role in leukemia and leukemia treatment is not well known.

Sorafenibisa multi-targeting tyrosine kinase inhibitor with activity against B-RAF and other kinases such as FLT3, VEGF, PDGF receptor and c-KIT; and is used for the treatment of various malignancies including AML and ALL [55]. It was used by Feldmann et al., to investigated whether Sorafenib interferes with necroptosis in apoptosis-resistant acute leukemia. Feldmann reported that Sorafenib inhibits necroptotic signaling and cell death in two models of necroptosis in acute leukemia by significantly reducingsecond mitochondria-derived activator of caspases (Smac) mimetic-induced necroptosis in apoptosis-resistant Acute Myeloid Leukemia (AML) cells. Also, Smac mimetic/Tumor Necrosis Factor (TNF) α -inducenecroptosisin FADD-deficient Acute Lymphoblastic Leukemia (ALL) cells which implies that Sorafenib may limit the anti-leukemic activity of anticancer drugs that trigger necroptosis under certain conditions, for example when caspase activation is blocked [56].

Further, Ponatinib is a multikinase inhibitor, which targets BCR-ABL besides other kinases such as VEGF receptor, PDGF receptor, FGFR, FLT3 and c-KIT [57] and it has been shown to inhibit both RIP1 and RIP3 via direct binding [58]. Ponatinib has been developed for the treatment of Philadelphia chromosome-positive acute leukemia [59]. The protective effect of Pazopanib, a receptor tyrosine kinase inhibitor that targets VEGF receptors, PDGF receptor and c-KIT [60] has been reported to be mediated via RIP1 as the main functional target [58]. Together, these data have shown that several multi-kinase inhibitors with different activity spectra can protect from necroptosis

by targeting RIP1 and/or RIP3, therefore can limit the anti-leukemic activity of necroptosis-inducing drugs in acute leukemia cells which has important implications.

In AML, it had been recently demonstrated that Smacmimetics alone or in combination with standard chemotherapeutic drugs such as cytarabine or epigenetic modifiers (i.e. demethylating agents, Histone Deacetylase (HDAC) inhibitors) can overcome apoptosis resistance of AML cells by inducing necroptosis as an alternative mode of programmed cell death [61-64]. Also, Smacmimetics together with glucocorticoids, demethylating agents or TNF α have been shown to elicit necroptosis in apoptosis-resistant ALL cells [65-67].

Induction of cell death is an important strategy for killing cancer cells. Via the treatment of cancer, the cancerous cells develop resistance to apoptosis via defective caspase activity owing to gene mutations or silencing. Since the necroptosis tends to occur in the absence of caspase activation, it is conceivable that necroptosis is an alternative mode of cell death to overcome apoptosis resistance in leukemia cells. Therefore, triggering necroptosis may represent an attractive new strategy for apoptosis-resistance leukemia as well as cancer.

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