

Role of apoptosis repressor with caspase recruitment domain (ARC) in cancer (Review)

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Abstract. Apoptosis repressor with caspase recruitment domain (ARC) is a potent inhibitor of apoptosis. Under physiological conditions, ARC is abundantly expressed in terminally differentiated cells, including cardiomyocytes, skeletal muscles and neurons. ARC serves a key role in determining cell fate, and abnormal ARC expression has been demonstrated to be associated with abnormal cell growth. Previous studies have revealed that ARC was upregulated in several different types of solid tumor, where it suppressed tumor cell apoptosis. Furthermore, the increased expression levels of ARC in cancer cells contributed to the development of therapeutic resistance and adverse clinical outcomes in patients with leukemia. However, the exact role of ARC, as well as the underlying molecular mechanisms involved, remain poorly understood. The present review summarizes the characteristics of ARC and its cytoprotective role under

different conditions and describes the potential ARC as a new target for cancer therapy.

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1. Introduction

Apoptosis is a physiological form of programmed cell death (1) and is characterized by cell contraction, DNA fragmentation and the apoptotic body formation. Apoptosis is involved in the regulation of the biological processes that serve important roles in tissue development, homeostasis and disease (2). Numerous studies have demonstrated that dysregulation of apoptosis is associated with the development of several diseases, including neurological disorders (3), cardiovascular diseases (4), autoimmune diseases (5) and cancer, including colon cancer (6) and lymphoma (1). It has been reported that apoptosis is increased during hypertrophy and myocardial infarction (7). By contrast, decreased activation of apoptosis is associated with several different types of cancer, such as lung cancer (8) and breast cancer (9).

Apoptosis is a complex process that is regulated by the interaction between pro- and anti-apoptotic proteins. It has been revealed that the upregulation of anti-apoptotic proteins prevents apoptosis and allows the proliferation of cancer cells (6,8).

Apoptosis repressor with caspase recruitment domain (ARC), an endogenous anti-apoptotic protein, is abundantly expressed in terminally differentiated cells such as neurons, and cardiomyocytes (10). However, previous studies have reported that ARC is upregulated in several different types of human cancer and promotes tumor cell survival, and

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Abbreviations: ARC, apoptosis repressor with caspase recruitment domain; NOL3, Nucleolar protein 3; Fas, Fas cell surface death receptor; FADD, Fas-associated with death domain protein; DISC, death-inducing signaling complex; CK2, casein kinase 2; Kv, Voltage-gated K (+); $I_{K(V)}$, whole cell K_v currents; PUMA, p53-upregulated modulator of apoptosis; Drp1, dynamin-related protein 1; JNK, JunN-terminal kinase; p53, protein 53 or tumor protein 53; Bax, BCL2 associated X apoptosis regulator; FOXO3A, Fork head box O3; TNF- α , tumor necrosis factor α ; Ras, rat sarcoma; I/R, Ischemia/Reperfusion; SNX13, sorting nexin 13; CARD, caspase recruitment domain; P/E, Proline/Glutamate; AML, acute myeloid leukemia; DOX, doxorubicin; ER, endoplasmic reticulum

Key words: apoptosis repressor with caspase recruitment domain, apoptosis, cancer, cytoprotection, target therapy

contributes to tumor invasion, metastasis and chemoresistance (9,11). The present review summarizes the function of ARC with a particular emphasis on the role of ARC in cancer.

2. Molecular characteristics of ARC

The human ARC was identified and characterized by Koseki *et al* (10). ARC is encoded by the nucleolar protein 3 (NOL3, also known as NOP30) gene, which is located on chromosome 16 (12) (Fig. 1A). The coding region between exon 2 and 4 is translated to yield a peptide containing 208 amino acids with a relative molecular mass of ~22,629 Da (10,12). The 208 amino acids peptide comprises two characteristic domains; the caspase activation and recruitment and the C-terminal domains, which are rich in proline and glutamic acid (Fig. 1B). In 2015, Jang *et al* published the crystal structure of the caspase recruitment domain (CARD) at a resolution of 2.4 Å, and revealed that it contains 95 amino acids. The dimer structure consists of five-helix bundle, which may be required for its anti-apoptotic function (13). The CARD belongs to the death domain superfamily (14), which interacts with pro-apoptotic proteins such as caspase-8, caspase-2 (10), p53-upregulated modulator of apoptosis (PUMA) (11) and BCL2 associated X apoptosis regulator (Bax) (15). The C-terminal domain consists of 113 amino acids, which is responsible for binding Ca^{2+} (16), and tumor protein p53 (17), thereby suppressing apoptosis.

3. Tissue-specific expression and physiological functions of ARC in normal organs

The expression of ARC mRNA was initially identified in human tissues by Koseki *et al* (10) and it was revealed that ARC is primarily expressed in skeletal muscle and the heart, but not in other tissues such as the placenta, liver or kidney. In addition, other studies have reported that ARC is expressed in the brain (18), vascular smooth muscle (19), primary spermatocytes (20), granulosa cells (21), islet β -cells (22) and cochlear hair cells (23).

Anti-apoptotic effect of ARC. ARC serves a protective role against cellular stress and is involved in homeostasis and development (24,25). In a rabbit model of cardiac regional ischemia following reperfusion, rabbits overexpressing ARC exhibited decreased apoptosis in the left ventricle (24). In a murine pulmonary hypertension model, the vascular remodeling capacity of ARC-deficient mice was diminished and accompanied by enhanced apoptosis and decreased proliferation in response to chronic hypoxia-induced pulmonary hypertension (25). In chick embryo myocardial cardiomyocytes, ARC overexpression protected cells from oxidative injury and promoted their survival (26). H9c2 cells overexpressing ARC were significantly more resistant to hypoxia-induced apoptosis (27). In addition, enforced ARC overexpression significantly prevented doxorubicin (DOX)-induced cardiotoxicity (28). Overexpression of ARC remarkably suppressed whole cell K_v currents ($\text{I}_{\text{K}(\text{V})}$) in transfected H9c2 cells following treatment with staurosporine, an apoptosis inducer that increased $\text{I}_{\text{K}(\text{V})}$ in wild-type cells and induced apoptosis (29). These data suggest that ARC protects myocardial cells from stress-induced apoptosis as well as chemical toxicity.

In the liver, ARC overexpression completely blocked the hepatocyte apoptosis or necrosis regulated via the Fas cell surface death receptor (Fas)/tumor necrosis factor (TNF) signaling pathway (30,31). Furthermore, ARC overexpression protected muscle fibers from apoptosis induced by mechanical stress or oxidative damage (32). Inhibition of ARC promoted cell death by increasing the production of pro-apoptotic factors, decreasing the stability of mitochondrial membranes and increasing the level of reactive oxygen species (ROS) following neomycin injury (23).

ARC prevented β -cell apoptosis induced by several cell death inducers, including endoplasmic reticulum (ER) stress and palmitate, while depletion of ARC in isolated islets significantly increased apoptosis in palmitate-treated cells (22). ARC expression was previously documented in testicular tissue, regulating apoptosis of primary spermatocytes (20). It was reported that ARC antagonized the adverse effect of zoldronate in osteoblasts, promoted osteogenic growth and differentiation of osteoblasts, and decreased apoptosis (33).

Other functions of ARC. In addition to its antiapoptotic role, ARC participates in the regulation of cell differentiation and proliferation. Overexpression of ARC suppressed myogenic differentiation via caspase inhibition (34), whereas the absence of ARC altered fiber-type distribution, resulting in muscle atrophy and decreased force-generating capacity (35). Russell *et al* (36) demonstrated that mutations, which alter the post-translational modification of ARC, may lead to myoclonus.

4. Role of ARC in cancer

High levels of ARC expression have previously been reported in several different types of cancer, including primary human breast cancer, cervical carcinoma, gastric cancer and colon adenocarcinoma (14,37-39). Furthermore, the expression levels were not only associated with different types of cancer, but also with sex, age, and tumor grade and size (37). Additional reports revealed that ARC is highly expressed in non-small cell lung cancer cells, PC-3 prostate cancer cells and renal cell carcinoma cells (40-42).

ARC-induced chemoresistance. ARC expression in cancer cells has been associated with increased chemoresistance. High expression levels of ARC in breast cancer cells promoted tumor growth, invasion and metastasis, and augmented chemoresistance (9,43). A high expression level of ARC in colorectal cancer liver metastasis enhanced the anti-apoptotic ability of colorectal cancer (37). ARC is highly expressed in newly diagnosed acute myeloid leukemia (AML) samples and has been demonstrated to decrease apoptosis induced by cytarabine and other agents. ARC may therefore contribute to drug resistance and increase survival time of leukemia cells (44-46). The high expression of cytoplasmic and nuclear ARC in nasopharyngeal carcinoma tissues are correlated with advanced local invasion. Overexpression of ARC in NPC 6-10B cells plays an important role in X-radiation and cisplatin resistance, and prolongs NPC cells survival by blocking the activation of caspase-8 and caspase-2 (47).

Chen *et al* (48) revealed that Me1007 cells overexpressing ARC inhibited caspase-8 activation, while another study indicated that ER stress-induced apoptosis (49). Carter *et al* (50)

transplanted ARC-knockdown AML cells into mice and demonstrated a significantly lower leukemia burden, increased survival rate and enhanced sensitivity to chemotherapy compared with controls. Conversely, ARC upregulated prostaglandin E2/ β -catenin production in the tumor microenvironment and augmented chemoresistance in AML cells (50). Huang *et al* (51) reported that increased ARC expression levels inhibited apoptosis in colon cancer. The aforementioned studies demonstrated that ARC serves an important role in the survival of cancer cells and chemotherapy resistance.

5. Molecular regulation of ARC expression

The expression level of ARC in tissues and cells is regulated by a number of factors, including post-transcriptional splicing, modification and degradation (43,52,53).

Upregulation of ARC expression. Rat sarcoma (Ras) controls ARC levels by transcriptional regulation and maintaining protein stability. Ras activates the *Nol3* promoter in a MEK/ERK-dependent manner and significantly increases the production of ARC mRNA. Furthermore, Ras prevents ARC degradation via the ubiquitin-proteasome pathway (43). The transcription factor fork head box O3 (FOXO3A) expressed in cardiomyocytes and skeletal muscle cells activates ARC expression by directly binding and trans-activating its promoter (52). ARC protein levels in muscle are increased as a result of endurance training; exercise resulted in a 37.5% increase in ARC protein levels (53) (Fig. 2).

Downregulation of ARC expression. Death signals induced by hypoxia (27,54), ischemia-reperfusion (I/R) (14,55), and other forms of stress (14,55-57) have been revealed to significantly decrease ARC levels. ARC contains lysine residues at positions 17, 68 and 163. The decrease in ARC levels during apoptosis are mediated by the decreased stability of the ARC protein, an effect indicated to be mediated by ubiquitin-proteasomal-mediated degradation (55,57). Previous studies have revealed that specific microRNAs (miRNAs/miRs) the decreased the expression level of ARC directly or indirectly (39,58,59). ARC mRNA 3'-untranslated regions contain two miR-185 binding sites. miR-185 modulates ARC expression at the post-transcriptional level and negatively regulates ARC expression (39). miR-30d downregulates FOXO3A and inhibits ARC expression (58). miR-155 directly decreases the expression of FOXO3A and its downstream protein ARC, and may cause renal proptosis under ischemia/reperfusion injury conditions (59). p53 serves an important role in decreasing the expression and transcription of ARC as well as promoting ARC degradation via p53-induced ubiquitin E3 ligase (57,60). A previous study revealed that oxidative stress enhanced post-transcriptional degradation of ARC via the ubiquitin-proteasome pathway (61). Sorting nexin-13 (SNX13), a potent mediator of heart failure, was revealed to directly modulate ARC stability and promote ARC degradation, thus increasing the apoptotic death of cardiomyocytes (62) (Fig. 2).

Post-translational regulation of ARC. A previous study revealed that the ARC protein had a molecular weight of ~34 kDa in human skeletal muscle and various adherent

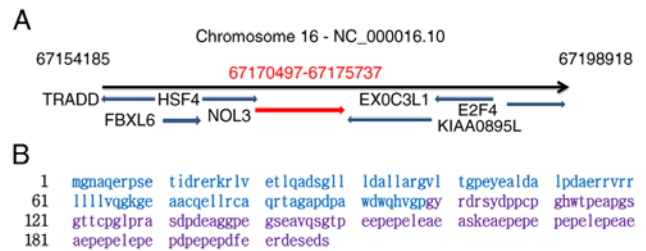


Figure 1. Coding gene location and amino acids sequences of ARC. (A) The location of *NOL3* coding gene on chromosome 16, highlighted in red. (B) Amino acids sequences of *NOL3* coding (ARC), ARC contains two domains, CARD domain amino acids sequences (highlight with blue), P/E domain amino acids sequences, highlighted in purple. ARC, apoptosis repressor with caspase recruitment domain; NOL3, nucleolar protein 3; CARD, caspase recruitment domain; P/E, Proline/Glutamate.

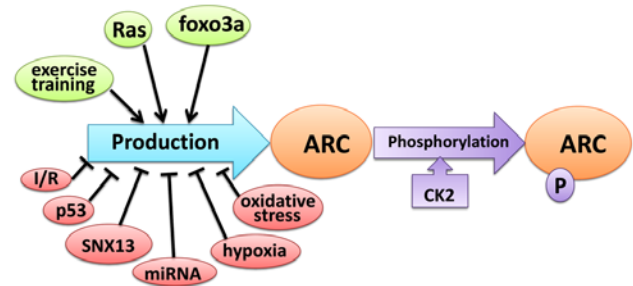


Figure 2. Regulatory factors of ARC. The factors that can either enhance ARC expression or prevent its degradation, are presented in green. The factors that can either inhibit ARC expression levels or promote its degradation, are presented in pink. The phosphorylation reaction of ARC regulated by CK2 are presented in lilac. ARC, apoptosis repressor with caspase recruitment domain; Ras, Rat sarcoma; FOXO3A, Fork head box O3; I/R, Ischemia/Reperfusion; SNX13, Sorting Nexin 13; p53, protein 53 or tumor protein 53; CK2, casein kinase 2; P, phosphorylation.

human cancer cell lines, and 38 kDa in human lymphoma cell lines (63). McMillan *et al* (64) revealed that ARC extracted from normotensive rats had a molecular weight of ~30 kDa, compared with 32 kDa in a spontaneously hypertensive rat. This shift in molecular weight suggested that the ARC protein may undergo post-translational modifications in different and cell types. Li *et al* (62) reported that ARC mRNA levels did not differ between cardiac tissues extracted from rats with heart failure and controls or between SNX13-deficient neonatal rat ventricular myocytes and normal cardiomyocytes, suggesting that the regulation of ARC expression begins at the posttranscriptional level. Dowds *et al* (65) revealed that during the serum withdrawal stage in an *in vitro* culture, post-translational regulation increased ARC stability and lead to its accumulation in the nucleus, which promotes cell survival (Fig. 2). Phosphorylation is a functional post-transcriptional modification and Li *et al* (66) revealed that casein kinase 2 (CK2), is a serine/threonine protein kinase that phosphorylates ARC at threonine 149. T149 phosphorylation directs ARC to the mitochondria and allows ARC to exert its anti-apoptotic effects (Fig. 2).

6. Cytoprotection and anti-apoptosis mechanisms of ARC

Apoptosis is controlled by an extrinsic pathway that originates from cell-surface receptors, and an intrinsic pathway that

involves the mitochondria and ER (1). The extrinsic pathway is mediated by death receptors (67) and death-associated domains (68). The intrinsic pathway is activated by varied stimuli, including metabolic, oxidative, proteotoxic stress and ROS (69). The extrinsic and intrinsic pathways activate caspases, which cleave multiple cellular proteins to induce cell apoptosis (70). ARC exhibits its cytoprotective and anti-apoptotic effects by inhibiting the extrinsic and intrinsic apoptotic pathways.

ARC inhibits the extrinsic apoptotic pathway. ARC inhibits the extrinsic pathway by interacting with Fas and Fas associated via the death domain. This subsequently prevents the homotypic interactions required for the assembly of the death-inducing signaling complex, which is important for the activation of caspases and further apoptotic signaling (14). A previous study revealed that ARC selectively interacts with the apoptosis initiator caspase-2 and caspase-8 and attenuates death receptor-induced apoptosis, involving the Fas cell surface death receptor, TNF receptor superfamily member 1A and TNF receptor superfamily member 25, or adaptor-induced apoptosis, involving TNFRSF1A associated via death domain and CASP8 and FADD like apoptosis regulator (10). Ekhterae *et al* (29) suggested that upregulation of ARC decreases $I_{K(V)}$ density and inhibits the staurosporine-induced $I_{K(V)}$ increase in cardiomyocytes, thereby enhancing survival and attenuating apoptosis by inhibiting K_v channel activity (29) (Fig. 3, Table I).

ARC antagonizes the intrinsic apoptotic pathway. ARC antagonizes the intrinsic pathway by interacting with apoptosis-associated proteins (11). The binding of ARC and Bax, which can inhibit Bax activation and accumulation in the mitochondria (15), increases the Bcl2 apoptosis regulator/Bax ratio (71,72), stabilizes the mitochondrial membrane and prevents cytochrome c release (27,73,74). Furthermore, ARC is also involved in the regulation of mitochondrial dynamics. For instance, ARC interacts with PUMA via its N terminus, and suppresses PUMA-mediated translocation of density regulated re-initiation and release factor in mitochondria, preventing mitochondrial fission and subsequent apoptosis (11).

miR-532-3p negatively regulates ARC expression and sensitizes cardiomyocytes to DOX-induced mitochondrial fission and apoptosis (75). It has been reported that ARC participates in cardioprotection and suppresses apoptosis caused by hypoxia and reoxygenation by preventing cytochrome c release from the mitochondria in a caspase-independent pattern (27,76). Furthermore, ARC overexpression prevented oxidative stress-induced cell apoptosis by protecting mitochondrial function independently of caspase inhibition, suggesting that ARC may act on a mitochondrial level (56).

ARC interacts with protein kinase RNA-like ER kinase and binds inositol-requiring protein 1 α , which prevents C/EBP homologous protein induction, diminishes the ER stress response and blocks Ca^{2+} release from ER (22). Furthermore, ARC not only blocks Ca^{2+} release but also binds Ca^{2+} through its C-terminal P/E-rich domain. Therefore, ARC suppresses intracellular Ca^{2+} increase and further prevents Ca^{2+} mediated apoptosis (16).

The proline-glutamic acid-rich region of ARC could bind with and negatively regulate p53 by inhibiting its transcriptional function, tetramerization and causing its cytoplasmic localization, thereby preventing p53 transfer into the nucleus and abrogate p53-induced apoptosis (17).

ARC binds with and prevents the activation of JUN N-terminal kinase (JNK), inhibiting cell death dependent on the JNK signaling pathway (30,77,78). ARC blocks acetaminophen-induced hepatic damage by antagonizing the JNK signaling pathway and preventing ROS production (77). ARC decreases amyloid-induced JNK phosphorylation, and ARC upregulation decreases β -cell apoptosis induced by activation of the JNK signaling pathway (78). Furthermore, ARC blocks Fas- and TNF-regulated cell death by JNK-dependent or independent pathways (30) (Fig. 3, Table I).

ARC inhibits apoptosis induced by death receptor activation (10), oxidative stress (14), serum deprivation (27), ischemia-reperfusion (56), doxorubicin and γ -radiation (79). ARC is a potent anti-apoptotic protein that prevents permeabilization of the mitochondrial outer membrane and decreases pro-apoptotic protein release and DNA fragmentation (64).

7. ARC will be a new target cancer therapy

Increased ARC expression has been documented in several types of cancer cells, including colon cancers (6), lung cancer (8), leukemia (44), glioblastoma (80). ARC upregulation contributes to chemotherapy and radiation resistance (11,81). Consistent with its role as an anti-apoptotic protein, ARC upregulation is associated with cancer grade and poor prognosis. For example, patients with AML with high ARC expression levels exhibited a poor chemotherapeutic response (82), while those with low ARC expression levels had an increased survival time (45), suggesting that ARC may have prognostic and therapeutic value in AML (46). ARC promotes multiple aspects of breast carcinogenesis, such as tumorigenesis, invasion, metastasis and chemoresistance. Therefore, ARC may serve as a novel therapeutic target for the development of future breast cancer therapies (9).

The antiapoptotic capacity of ARC may be regulated by certain miRNAs and enzymes. miR-185 targets ARC, decreases its anti-apoptotic function and increases apoptosis in gastric cancer cells (39). Phosphorylation of ARC by CK2 contributes to chemotherapy resistance by inhibiting DOX-induced apoptosis; whereas, CK2 inhibitors increase the sensitivity of cancer cells to DOX by inhibiting the phosphorylation of ARC (83). These data suggest that ARC can be used as a novel drug target in cancer treatment (84).

In summary, ARC is an important regulator of apoptosis and is associated with several human diseases, particularly cancer. Therefore, ARC may serve as a novel drug target in cancer treatment. Furthermore, miRNAs and enzyme inhibitors may target and prevent ARC from exerting its anti-apoptotic function directly or indirectly (13).

8. Conclusion

Apoptosis is an important regulator of tissue and developmental homeostasis. Furthermore, apoptosis is associated with the pathogenesis of a large number of diseases, including

Table I. ARC binding proteins and their functions mediated by binding to ARC.

Interactant	ARC-mediated function	(Refs.)
Fas/FADD	Precludes the conventional homotypic interactions required for DISC	(14)
caspase-2/caspase-8	Attenuate apoptosis	(10)
K _v channel protein	Decreases I _{K(V)} density and attenuates cardiomyocyte apoptosis	(29)
PUMA	Inhibits PUMA-mediated Drp1 translocation in mitochondria and the consequent mitochondrial fission	(11)
JNK	Diminishes JNK pathway activation and apoptosis	(77,78)
p53	Negatively regulate p53 by inhibiting its transcriptional function, tetramerization and triggering its cytoplasmic localization	(17)
Ca ²⁺	Suppresses the intracellular Ca ²⁺ increase and blocks Ca ²⁺ -mediated apoptosis	(16)
Bax	Prevents Bax activation and accumulations in mitochondria	(15)

ARC, apoptosis repressor with caspase recruitment domain; Fas, Fas cell surface death receptor; FADD, Fas-associated with death domain protein; DISC, death-inducing signaling complex; I_{K(V)}, whole cell K_v currents; PUMA, p53-upregulated modulator of apoptosis; Drp1, dynamin-related protein 1; JNK, JunN-terminal kinase; p53, protein 53 or tumor protein 53; Bax, BCL2 associated X apoptosis regulator.

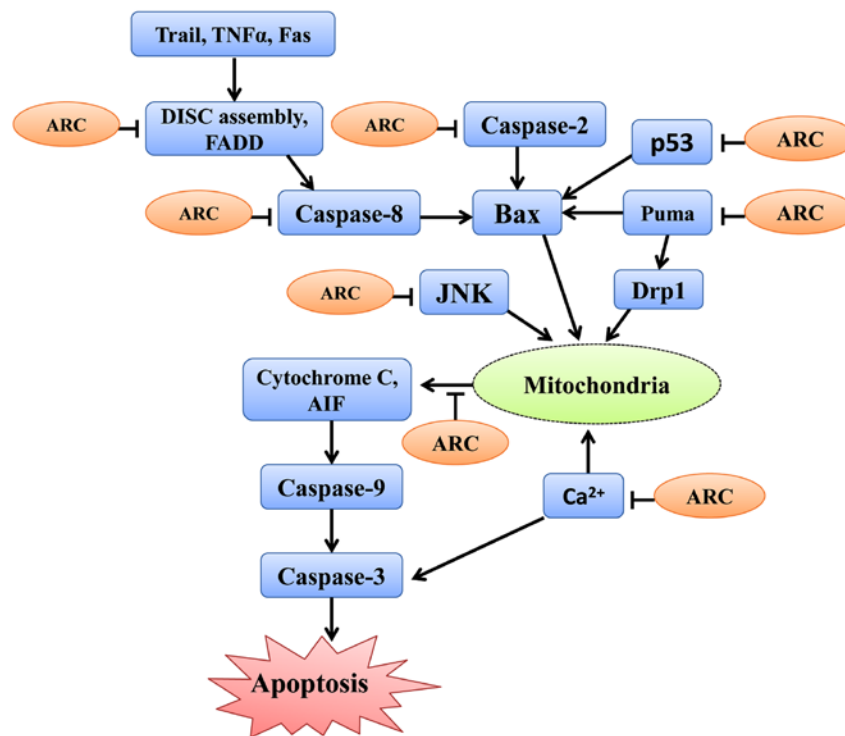


Figure 3. Roles of ARC in regulating the anti-apoptosis pathways. The pathways were simplified in the diagram. The diagram presents the key components and the reactions of apoptosis pathways that are interfered by ARC. ARC, apoptosis repressor with caspase recruitment domain; Fas, Fas cell surface death receptor; FADD, Fas-associated with death domain protein; DISC, death-inducing signaling complex; Trail, TNF-related apoptosis-inducing ligand; PUMA, p53-upregulated modulator of apoptosis; Drp1, Dynamin-related protein 1; JNK, Jun N-terminal kinase; p53, protein 53 or tumor protein 53; Bax, BCL2 associated X apoptosis regulator; TNF- α , tumor necrosis factor α ; AIF, apoptosis inducing factor.

autoimmune diseases, viral infection, degenerative disorders and cancer (85,86). Cancer results in significant morbidity and mortality and is a significant public health problem worldwide (87-89). The currently used chemotherapeutic drugs are cytotoxic agents that have various side effects (90). Therefore, there is a requirement for the development of targeted and more effective treatment options with fewer side effects. ARC has been revealed to decrease cell death

in various different types of cell by binding and inactivating components of the apoptosis pathways. Upregulation of ARC is highly associated with tumorigenesis and chemotherapy resistance; therefore, inhibiting the expression of ARC in cancer cells may increase the efficacy of anti-cancer drugs (45). Future studies are required to investigate how to effectively deliver targeted ARC inhibitors for the treatment of cancer.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

ZY, LA and PL designed the review and edited the manuscript. ZY, QL and YA wrote the manuscript. XC, ZQL, ZL and JG collected and analyzed data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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