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Review

Advances in the knowledge on the role of apoptosis repressor with caspase recruitment domain in hemorrhagic stroke

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ABSTRACT

The apoptosis repressor with caspase recruitment domain (ARC) plays a critical role in extrinsic apoptosis initiation *via* death receptor ligands, physiological stress, infection response in a tissue-dependent manner, endoplasmic reticulum (ER) stress, genotoxic drugs, ionizing radiation, oxidative stress, and hypoxia. Recent studies have suggested that regulating apoptosis-related pathways can improve outcomes for patients with neurological diseases, such as hemorrhagic stroke. ARC expression is significantly correlated with acute cerebral hemorrhage. However, the mechanism by which it mediates the anti-apoptosis pathway remains poorly known. Here, we discuss the function of ARC in hemorrhagic stroke and argue that it could serve as an effective target for the treatment of hemorrhagic stroke.

Introduction

Hemorrhagic stroke usually refers to non-traumatic spontaneous hemorrhage in the brain parenchyma, including subarachnoid hemorrhage and intracerebral hemorrhage.[1] Its global incidence rate is gradually increasing, especially in low- and middle-income countries.[2] Hemorrhagic stroke develops rapidly and is often clinically accompanied by severe headaches, increased intracranial pressure, brain herniation, respiratory failure, disturbance of consciousness, and immunosuppression.[3], which seriously threatens the life and health of patients.[3] Moreover, post-hemorrhagic stroke brain injury can lead to neurological dysfunction through a mechanism closely related to inflammation, oxidative stress, mitochondrial dysfunction, autophagy, and apoptosis.[1,4,5]

Microglia are inflammatory cells considered early responders in pathological stimuli after cerebral hemorrhage.[6] Activated microglia can adopt two phenotypes (M1 and M2)[7,8], which dynamically participate in the damage and repair of brain tissue after a hemorrhagic stroke. Additionally, reactive oxygen species can alter the cellular membranes and hinder genetic material synthesis, leading to neuronal damage and even death in hemorrhagic stroke patients.[4] Moreover, neuronal autophagy is activated in hemorrhagic stroke and participates in this pathophysiological process. Autophagy mainly exerts a degradation effect by activating inflammasomes consisting of a cytosolic pattern-recognition receptor, an adaptor protein, and an effector component.[9] Altogether, the outcome of hemorrhagic stroke depends on a delicate balance between the recovery and pathology pathways. If the injury process is faster than recovery, the body may initiate cell death mechanisms (apoptosis, necrosis, and autophagy).[10] and then actively eliminate apoptotic cells.[11]

The cysteine-aspartic protease (Caspase) family plays an important role throughout the programmed cell death process by interacting with numerous activators or inhibitors.[12,13] Caspases are divided into two categories based on their *N*-terminal pro-domain function and amino acid length: initiator Caspases (Caspase-8, −9, and-12) and effector Caspases (Caspase-3, −6, and-7).[14] Meanwhile, apoptosis repressor with caspase recruitment domain (ARC) is an endogenous anti-apoptotic protein containing a proline- and glutamate-rich *C*-terminal region and an *N*-terminal caspase recruitment domain (Pro-domain) of 23–

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219 amino acids.[15] It was initially shown to specifically inhibit Caspase-2 and Caspase-8, thus blocking apoptosis[16,17]. Moreover, ARC is essential for apoptosis and necrosis regulation and is related to many human diseases, and may thus be an optimal target for therapeutic intervention.[18–20]

The Molecular Characterization of ARC

ARC is a protein with an anti-endogenous apoptosis function, and its anti-apoptotic effect depends on its structural and functional domains. As an apoptosis regulation protein, ARC plays a strong cardioprotective role during myocardial injury.[21] and is also found in the brain.[22], granulosa cells.[23], islet β-cells[24,25], and liver cells.[26,27] Furthermore, ARC expression levels in the mouse cortex may decrease with age.[28] In a mouse model, long-term drinking decreased the expression of ARC in the cerebellum, which may be related to the increased cerebellar cell apoptosis induced by alcohol consumption.[29] In addition, ARC can also inhibit the amyloid-induced activation of the c-Jun N-terminal kinase (JNK) pathway and apoptosis in β cells, thereby reducing the loss of β cells in patients with type 2 diabetes.[25] Additionally, the protein transduction of ARC can directly inhibit JNK and JNK-dependent tumor necrosis factor α production, thus saving mice from fulminant liver failure.[26] Previous studies have mainly demonstrated that ARC exerted its anti-apoptotic effects by either directly binding to Caspase-2 and −8 or by indirectly decreasing mitochondrial Ca^{2+}[30] However, other potential molecular features and functions of ARC need to be further studied and explored.

Cytoprotection and Anti-apoptosis Mechanisms of ARC

Currently, ARC is known to be involved in two classical apoptosis pathways in the cytoplasm, namely the extrinsic pathway (mediated by death receptors) and the intrinsic pathway (mediated by mitochondria).[31] Mitochondrial apoptosis is mainly regulated by B-cell lymphoma-2 (Bcl-2) family proteins, which can have pro-apoptotic effects (e.g., Bax, Bok) or anti-apoptotic effects (e.g., Bid, Bcl-2).[32] During the response to danger signals or stress, the levels of expression and activation of Bcl-2 family members determine whether programmed cell death is initiated or inhibited.[32,33] Members of this protein family control neuronal apoptosis by acting on the integrity and energetics of the mitochondrial outer membrane, and they regulate Ca^{2+} homeostasis in mitochondria and the endoplasmic reticulum. Several studies have shown that the deletion of a single pro-apoptotic gene, Bax, can exert a neuroprotective effect.[34] When a pro-apoptotic protein is released into the cytoplasm, it initiates the caspase cascade. Caspase-3 is the last executive enzyme in the apoptosis cascade; it cleaves proteins, enzymes, and nucleotides, leading to cell homeostasis disorders, and resulting in cell death.[35,36] During apoptosis, the cell membrane structure is retained until the end of the process.[37] Concurrently, ARC can also directly bind to p53 and other apoptosis regulatory factors and release Bcl-2, exerting an intrinsic anti-apoptotic function.[38] In summary, ARC is a unique inhibitor of death in the central nervous system because of its key role in both intracellular and extracellular apoptotic pathways.

Research Progress on the Caspase Recruitment Domain in Hemorrhagic Stroke

Apoptosis in hemorrhagic stroke

It is generally believed that cell death occurs after contact with blood metabolites or damaged cells. Recent research demonstrated that programmed cell death, especially apoptosis, plays a vital role in the pathophysiology of hemorrhagic stroke.[39] During hemorrhagic stroke, apoptosis mainly occurs in central nerve cells, such as microglia and cerebral vascular endothelial cells. In the early hemorrhagic stroke stage, a series of pathophysiological events, such as energy failure, excitotoxicity, oxidative stress, inflammation, and finally, apoptosis, lead to neuronal cell death after hours or days.[40] Moreover, the severity of this disease depends on the duration, severity, and location of the hemorrhagic stroke within the brain.[41] Interestingly, the markers of apoptosis and necrosis can appear in the same cell at the same time, indicating that multiple death programs may occur simultaneously. However, the exact mechanism of these new types of cell death remains unclear. Recent studies have shown that regulating the toll-like receptor 4 (TLR4) signaling pathway can mediate nerve cell apoptosis. Jung et al.[42] found that activating two TLR4-related signaling pathways could induce apoptosis in microglia. In addition, Wang et al.[41] found that TLR4 could upregulate matrix metallopeptidase 9 (MMP-9) expression and initiate apoptosis by binding to high mobility group box 1 (HMGB1), opening the signal transduction pathway in a subarachnoid hemorrhage model. However, after low-dose lipopolysaccharide pretreatment, activation of the TLR4 signal pathway down-regulated MMP-9 and Caspase-3 expression, thus inhibiting apoptosis and exerting neuroprotection. Moreover, the Fas/FasL signaling pathway also participates in persistent apoptosis, and it triggers the production of pro-inflammatory cytokines through external apoptosis signal cascades.[43] Additionally, the hematopoietic growth factor erythropoietin inhibits apoptosis and protects neurons from ischemic damage.[44] These findings suggest that death receptors participate in apoptosis induction after a hemorrhagic stroke, and their inhibition may improve neuronal survival.

In recent years, research about anti-neuronal apoptosis drugs has also made significant progress. For example, ginsenoside Rg1 can significantly inhibit apoptosis in cerebral cortex neurons.[45] Overall, physiological and pharmacological inhibitors targeting apoptosis may be an important part of this new treatment strategy against early brain injury caused by hemorrhagic stroke.

Role of ARC in hemorrhagic stroke

Two types of caspases regulate apoptosis: promoters and effectors. Promoter caspases activate effector caspases by cleavage of the inactive form. Then, the effector caspases (e.g., Caspase-3 and −7) activate endonucleases, resulting in DNA cleavage, eventually destroying the whole cell structure.[46] In some cases, apoptosis can also be triggered in a caspase-independent manner.[47] Although apoptosis is not a new concept, the complex mechanisms of apoptosis in hemorrhagic stroke are still being explored (Figure 1). Some studies have shown that caspase-dependent cascades are crucial for local hemorrhagic

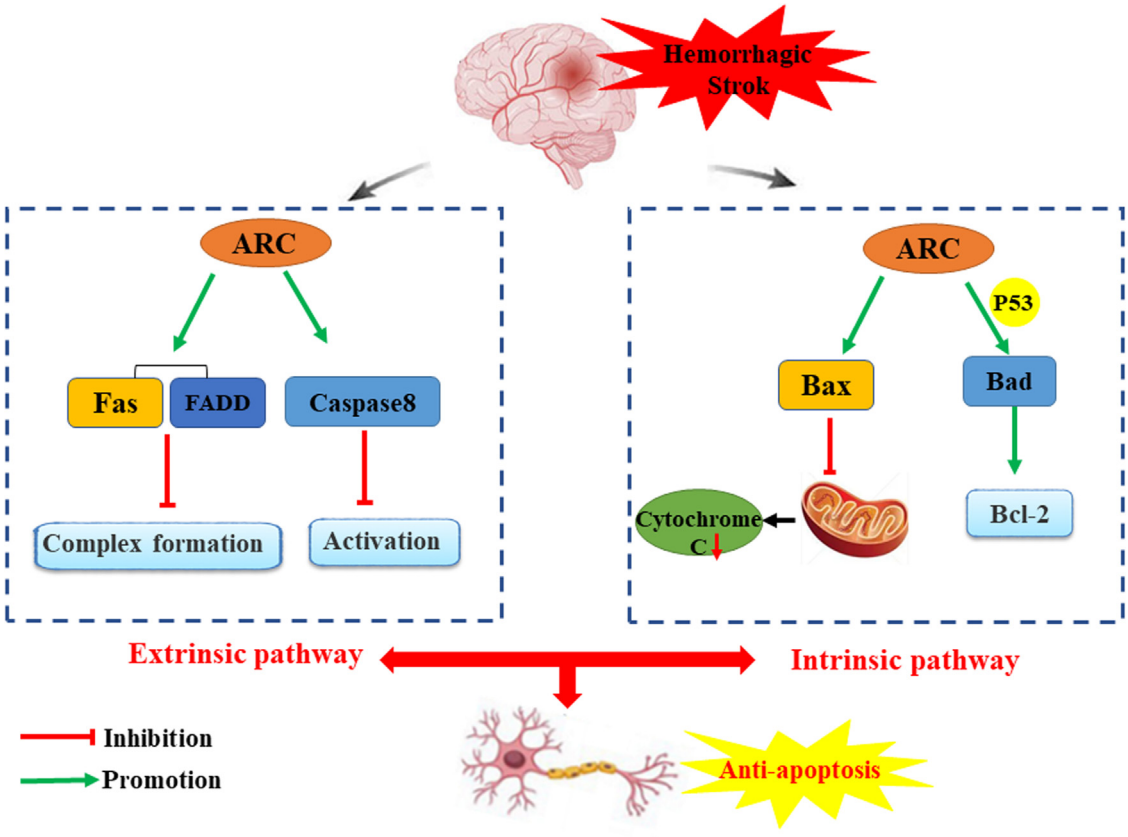

Figure1. Role of ARC in hemorrhagic stroke. ARC has a key role in two classical apoptosis pathways. One is an extrinsic pathway mediated by death receptors, the other is an intrinsic pathway mediated by mitochondria.
ARC: Apoptosis repressor with caspase recruitment domain; Bax: BCL2-associated x apoptosis regulator; FADD: Fas-associated with death domain protein; Fas: Fas cell surface death receptor; p53: Protein 53.

injury, whereas caspase-independent cascades are more involved in neurotoxin-induced apoptosis.[48] Hemorrhagic stroke is an acute and critical neurovascular and cerebrovascular disease. Many studies have shown that regulating apoptosis-related pathways can improve the outcome of central nervous system diseases, including hemorrhagic stroke.[19,49] ARC is widespread in neurons and protects them by inducing the rapid proteasome degradation of receptor-interacting protein kinase 3, weakening the response to hemorrhagic/ischemic death signals.[50] A study found that cerebral injury significantly decreased ARC expression in the hippocampal CA1 region in a time-dependent manner. Therefore, neuronal death caused by ischemia/hypoxia may occur through the down-regulation of ARC in hippocampal neurons.[50] However, most of these results are preliminary, and further clinical studies are needed to determine whether ARC plays a pathological and physiological role in preventing apoptosis after cerebral hemorrhage injury.

Hemorrhagic stroke in translational research

Finding more effective therapeutic methods requires a deeper exploration of the application prospect of ARC in the treatment of hemorrhagic stroke from the perspective of transformation. As research on the mechanisms of hemorrhagic stroke has progressed, many clinical trials on new therapeutic strategies offer real hope for hemorrhagic stroke patients. Unlike prior studies, an increasing amount of research has focused on drugs enhancing the organism's defense mechanisms, such as defense responses, inflammation, and immune responses. This represents an extremely significant advance over earlier studies. For instance, sulforaphane, a component of broccoli, is a strong nuclear factor erythroid 2-related factor 2 (Nrf2) activator and protects the nervous system from many diseases through the Nrf2 pathway, including brain injury in hemorrhagic stroke.[51] Furthermore, peroxisome proliferator-activated receptor-γ (PPAR-γ) agonist exerts its positive activity through upregulating cellular defenses.[52] Therefore, the study of ARC-related clinical drugs and combined therapy against apoptosis may be one of the best ways to reduce cerebral hemorrhage injury.

ARC in other diseases

Besides maintaining the normal development of the body and the stability of the internal environment, ARC affects the pathophysiology of other diseases.[15] Numerous studies have suggested that it can inhibit apoptosis in various diseases in a variety of ways (Table 1), and has the potential as a treatment target.

ARC and myocardial ischemia/reperfusion injury (MI/RI)

As a powerful cardioprotective factor, ARC plays an important protective role in mediating anti-apoptosis and improving cardiac function after MI/RI.[53] Recent studies

Table 1
The role of ARC in other diseases.

Disease	Corresponding targets	Signaling pathway	Effector cells	ARC-mediated function	References
MI/RI	Bcl-2/Bax	ER stress/CHOP signaling	Cardiomyocytes	Prevent cardiomyocyte apoptosis	[53]
MI/RI	Caspase-2	Mitochondrial pathway	Cardiomyocytes	Against oxidative stress-induced apoptosis	[54]
MI/RI	Mineralocorticoid receptor antagonists	Ubiquitin-proteasome pathway	Cardiomyocytes	Inhibit cardiomyocyte apoptosis	[55]
Heart failure	SNX13	SNX13-PXA-ARC-caspase	Cardiomyocytes	Neutrophil infiltration, neuronal injury, and death	[57]
Heart failure	miR-223	CircHRCR/miR-223/ARC	Cardiomyocytes	Attenuate apoptosis and prevent heart failure	[58]
Colon cancer	TRAF6	NF-κB signaling	T cells	As a critical protector	[61]
AML	ARC	MAPK/PI3K	Mesenchymal stem cells	ARC confers drug resistance and survival advantage	[62]

AML: Acute myeloid leukemia; ARC: Apoptosis repressor with caspase recruitment domain; Bcl-2: B-cell lymphoma-2; CHOP: C/EBP homologous protein; ER: Endoplasmic reticulum; MI/RI: Myocardial ischemia/reperfusion injury; NB: Nuclear factor.

demonstrated that the caspase enrichment domain could protect cardiomyocytes from oxidative stress by inhibiting the Caspase-2-mediated mitochondrial pathway in a rat model of MI/RI, providing a new strategy for heart protection.[54] Additionally, ARC can regulate myocardial programmed necrosis and reduce the area of myocardial infarction by preventing the opening of the mitochondrial permeability transition pore (mPTP). Furthermore, low-dose aldosterone antagonists can cause ARC degradation *via* the ubiquitin-proteasome pathway, whereas spironolactone or eplerenone can reduce ARC degradation, thereby inhibiting cardiomyocyte apoptosis.[55] These results indicate that ARC may be an effective interventional target for the clinical prevention and treatment of MI/RI.

ARC and heart failure

Under pathological conditions, down-regulation of ARC expression may also lead to various heart diseases, such as heart failure. Representative studies have shown that 36.7% of terminal heart failure patients had reduced ARC protein expression in cardiac tissue[56] Li et al.[57] revealed that adenoviral-induced ARC overexpression could reduce the activity of caspases, thereby inhibiting exogenous and endogenous apoptosis in a heart failure mouse model. Confirming the anti-heart failure effect and mechanism of ARC in myocardial tissue, Wang et al.[58] showed that TgARC mice also had myocardial protection in the heart failure model. Moreover, miRNA-223, a positive regulator of heart failure, induced further deterioration in mice with heart failure by inhibiting the expression of its downstream target, ARC. These results confirm that ARC may be an attractive therapeutic target in heart failure therapy.

ARC and cancers

Most colon cancer cell lines and primary colon cancer have high ARC levels.[59,60] Furthermore, well-, moderately-, and poorly-differentiated cancer tissues had higher cytoplasm ARC levels than healthy tissues, suggesting that ARC may be a new marker of human colon cancer.[61] In recent years, studies have demonstrated that the down-regulation of ARC in various cancers could induce apoptosis and reduce chemotherapy resistance. This could thus become a new path to overcome chemotherapy resistance. Additionally, ARC can regulate cell death induced by the second mitochondrial cysteine protease mimic in acute myeloid leukemia (AML) through BIRC2/MAP3K14 signaling, indicating that ARC may improve the therapeutic potential of the cysteine protease mimic.[38] ARC derived from AML cells is upregulated by Mesenchymal stem cells (MSCs) through mitogen-activated protein kinase (MAPK) and phosphatidylinositide 3-kinases (PI3K) signaling pathways *in vitro* and *in vivo* Thus, AML survival advantages would be significantly increased by protecting them from apoptosis induced by chemotherapy and selective endogenous or exogenous apoptotic drugs.[62]

Conclusions

ARC is an important regulatory factor in the occurrence, development, and outcome of various diseases through its anti-apoptotic properties. The continuous clarification of the regulatory mechanisms of ARC and its upstream regulatory targets

in hemorrhagic stroke indicate that regulating ARC-mediated apoptosis can reduce neuronal damage, providing novel perspectives for clinical therapy strategies. Therefore, the anti-apoptotic effect of ARC makes it an effective target for neuronal protection. It is crucial to further explore and validate the role of ARC in hemorrhagic stroke, as this knowledge would lay a theoretical foundation for the scientific and rational formulation of prevention and control measures.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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