Review Article

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# Activating transcription factor 3, an early cellular adaptive responder in ischemia/reperfusion-induced injury

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## Abstract

Recent studies have reported that ischemia/reperfusion (I/R) may act in the immune system where an exaggerated inflammatory response is initiated. With the activation of the immune system, damage-associated molecular patterns migrate and adhere to the I/R region, consequently inducing multiorgan injury. Emerging data indicate that upon I/R, stress-inducible proteins, including activating transcription factor 3 (ATF3), play essential roles in signaling during antiapoptotic, antimigration, and anti-inflammatory processes. Accumulating data suggest that ATF3 may be a potential target in I/R- or inflammation-induced organ dysfunction. This minireview focuses on the emerging evidence of the roles of ATF3 in multiple organs including the kidney, myocardium, and brain following I/R injury. In addition, this review addresses the role of ATF3 in chronic inflammation-induced pathophysiologies such as diabetes and atherosclerosis.

**Keywords:** *Activating transcription factor 3, Ischemia, Reperfusion*

## Introduction

Reperfusion insult, called ischemia/reperfusion injury (IRI) or reoxygenation injury, is tissue damage caused when the blood supply returns to tissue (reperfusion) after a period of ischemia or lack of oxygen (anoxia or hypoxia). The absence of oxygen and nutrients from blood during the ischemic period creates a condition in which the restoration of circulation results in inflammation and oxidative damage through the induction of oxidative stress rather than (or along with) the restoration of normal function. Reperfusion of ischemic tissues is often associated with microvascular injury, and following reperfusion, activated endothelial cells produce more reactive oxygen species (ROS) but less nitric oxide. This imbalance results in an inflammatory response [1]. The inflammatory response is partially responsible for the damage caused by reperfusion injury. Under I/R conditions, many stress-inducible transcriptional factors, such as activating transcription factor 3 (ATF3), are expressed [2]. This review discusses the elevated ATF3 expression that accompanies IRI-induced increases in ROS and inflammation resulting from tissue injury.

## Activating transcription factor 3

ATF was discovered in 1987 [3], and full-length ATF3 was originally isolated from a serum-induced HeLa cell cDNA library using a DNA probe [4]. ATF3 has been implicated in the cellular response to various insults, including I/R of the kidney, heart, and brain [5,6]; liver damage [7]; ventilation-induced lung damage; and many types of insults to cultured cells, including hypoxia [8] and genotoxic agents such as doxorubicin, ultraviolet light, and ionizing radiation [9]. Many circumstances that cause ATF3 expression also lead to cell death [10,11]. However, ATF3 has also been found to be constitutively expressed in a number of human cancers, and it is associated with metastatic potential. ATF3 is believed to have at least two key roles: as a mediator of the cellular stress response and as a regulator of cell proliferation. However, because the functions of ATF3 depend on its transcriptional milieu, ATF3 can have opposite effects on different types of cells [12]. Both gene delivery [13] and gene inactivation experiments [14] have attributed proapoptotic effects to ATF3; however, antiapoptotic effects have also been described [15]. Similarly, ATF3 has been reported to suppress or promote cell cycle progression [9,16]. In addition, in recent years, its role in immune response pathways has received much attention, particularly its role as a negative regulator of Toll-like receptor (TLR) family signaling in the inflammatory response [17]. Network analysis has predicted that ATF3 is a part of a transcriptional complex containing members of the nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-κB) family and that ATF3 can regulate the expression of inflammation-related genes, including interleukin (IL)-1β, IL-6, IL-12,

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tumor necrosis factor (TNF)-α, and chemokine (C-C motif) ligand 4 [18]. A new adaptive pathway in which ATF3 has been implicated is the endoplasmic reticulum stress response (ERSR; also known as the unfolded protein response). ERSR occurs in response to the pathological accumulation of unfolded or misfolded proteins in the lumen of the endoplasmic reticulum (ER). ATF3 has also been implicated in the protein kinase RNA-like endoplasmic reticulum kinase-mediated pathway, which is initially protective but also has a role in inducing apoptosis through the ATF4–ATF3–C/EBP homologous protein cascade in affected neurons [19]. However, a causal link between the ERSR and ATF3 expression has not been established, and the effect of ATF3 on stressed cells is uncertain.

## Protective effects of activating transcription factor 3 against ischemia/reperfusion in the kidney

The protective effects of ATF3 against I/R in the kidney have been documented. A study confirmed that ATF3$^{-/-}$ mice exhibited higher rates of mortality, kidney dysfunction, inflammation, and apoptosis than wild-type mice following renal I/R, whereas the restoration of ATF3 expression through the adeno-associated virus in the kidney of ATF3$^{-/-}$ mice could protect these mice from I/R-induced injury. A previous study of ATF3 expression in renal epithelial cells indicated that ATF3 binds to the ATF/cyclic AMP (cAMP) response element-binding protein (CREB) sites in the promoter regions of the target genes, thereby inhibiting the binding of NF-κB; this inhibition suppresses the transcription of IL-6 and IL-12b [5]. The binding of ATF3 to the ATF/cAMP response element site of target genes such as IL-6 or IL-12 is related to ATF3-associated histone deacetylase (HDAC), which performs chromosomal remodeling and has an important role in the regulation of transcriptional activity [20,21]. Histone acetyltransferases mediate the acetylation of histones to unwind the chromatin structure, which provides access to positive transcriptional regulators and thereby promotes transcriptional activation. However, HDACs have the opposite effect, that is, they mediate chromatin condensation by repressing transcriptional activation, resulting in inaccessibility to gene promoters. Li *et al*. confirmed that ATF3-associated HDAC causes the condensation of the chromatin structure and blocks the binding of NF-κB to the promoter regions of IL-6, IL-12, TNF-α, and monocyte chemotactic protein (MCP)-1, inhibiting the transcription of these inflammatory factors and suppressing TLR4-associated inflammatory signaling pathways [2,5,22]. Furthermore, Chen *et al*. reported that during renal I/R-induced inflammation, the induction of the adhesion molecules P- and E-selectin, IL-6, intercellular adhesion molecules, vascular cellular adhesion molecules, and MCP-1 was enhanced in ATF3$^{-/-}$ mice compared with that in wild-type mice. An *in vitro* study showed that MCP-1 expression in epithelial cells and the migration of macrophages were inhibited by administration of exosomes containing epithelium-derived ATF3 RNA and that I/R-induced kidney injury was attenuated following the administration of these exosomes [23]. Regarding the regulation of ATF3 by microRNAs (miRs) in the kidney after I/R, miR-494 can bind to the 3'untranslated region of ATF3 and decreases its transcription [24], and miR-494 overexpression through lentivirus infection decreases the expression of ATF3 and induces the production of inflammatory mediators, such as IL-6, MCP-1, and P-selectin, after renal I/R, exacerbating apoptosis and further decreasing renal function [24]. Interestingly, Panich *et al*.[25] and Lan *et al*. showed that urinary exosomes containing ATF3 and urinary miR-494 are sources of urinary biomarkers of sepsis-related acute kidney injury and I/R. However, miR-494 is expressed earlier than ATF3 in kidney tissue following I/R in mice, and urinary miR-494 may precede the appearance of urinary exosomes containing ATF3 after renal I/R. Therefore, urinary miR-494 may be an early kidney I/R biomarker and may be a more effective biomarker than ATF3.

## Protective effects of activating transcription factor 3 against ischemia/reperfusion in the cardiovascular system

Only a few studies have investigated the role of ATF3 in myocardial IRI (MIRI). A recent study indicated that the number of inflammatory cells increased in ATF3-null hearts subjected to myocardial ischemic preconditioning and I/R [26]. The aforementioned study also suggested that ATF3 plays a cardioprotective role in MIRI; this cardioprotective role is probably related to TLR4-associated inflammatory signaling pathways or to the role of ATF4 in reducing ER stress-induced inflammation and apoptosis by catalyzing histone deacetylation. Furthermore, Brooks *et al*. observed an obvious increase in the number of inflammatory cells and neutrophils in ATF3-null hearts subjected to MIRI after ischemic preconditioning [26]. Although the genetic deletion of ATF3 did not decrease the inflammatory response and attenuated monocyte and neutrophil infiltration in nonpreconditioned hearts, it abolished the cardioprotective effects of ischemic preconditioning [26]. These results suggest that ATF3 negatively regulates the inflammatory response in MIRI.

Krivoruchko and Storey showed that ATF3 inhibited p53 transcription and suppressed myocardial apoptosis, resulting in a protective effect on the myocardium [27]. However, the overexpression of ATF3 through a transgenic strategy in specific heart tissues of mice led to altered α-skeletal actin gene expression and impaired cardiac function [28]. In summary, these results suggest that ATF3 plays a more important cardioprotective role after ischemic preconditioning than detrimental roles, thus to reduce heart injury. Previous studies have demonstrated that oxidative stress and inflammation-induced apoptosis play a fundamental biological role in MIRI [29] and that inflammation plays a major role in many cardiovascular events, including atherosclerosis, smooth muscle cell migration, oxidative stress, elastolysis, and collagen degradation resulting in the stiffening of large arteries. Atherosclerosis is a chronic inflammatory disease characterized by the accumulation of lipid-loaded macrophages in the arterial wall [30]. On atherosclerosis development, in vascular endothelial cells, ATF3/liver regenerating factor-1 is one of the early response genes that is activated in response to atherogenic stimuli [14].

In the pathogenesis of atherosclerosis, macrophages take up lipoproteins containing apolipoprotein B, such as low- and very-low-density lipoproteins, to form foam cells, inducing a more aggravated inflammation cascade [30]. In addition, Gold *et al*. used an analysis method integrating epigenomic and transcriptomic datasets with a transcription factor binding site prediction algorithm, which suggested that ATF3 regulates macrophage foam cell formation [31]. Moore and Fisher confirmed that the high-density lipoprotein (HDL) treatment of bone marrow-derived macrophages increased the expression of ATF3 mRNA and protein, and they showed that HDL downregulated the binding of ATF3 to promoters of cytokine genes [32]. Finally, they used ATF3-deficient mice to show that the HDL-mediated suppression of inflammatory mediator production was dependent on ATF3 *in vitro* and *in vivo*. These results define a previously unknown role of ATF3 in controlling macrophage lipid metabolism, demonstrating that ATF3 is a key intersection point for lipid metabolic and inflammatory pathways in atherosclerosis.

Another important inflammation-induced cardiovascular disease is neointima formation due to vascular smooth muscle cell (VSMC) proliferation. Lv *et al*. found that ATF3 expression in VSMCs was induced by various stimuli, including serum, angiotensin II, and $H_2O_2$ [16]. The knockdown of ATF3 induced the apoptosis of VSMCs, and the overexpression of ATF3 promoted the migration of VSMCs and induced the expression of matrix metalloproteinases 1, 3, and 13. These results suggest that ATF3 regulates the survivability of VSMCs. In addition, interferon regulatory factor 7 (IRF7), a member of the IRF family, plays crucial roles in innate immunity; it reduced neointima formation in smooth muscle cell-specific IRF7 transgenic mice compared with nontransgenic controls in response to carotid injury, whereas the global knockout of IRF7 resulted in the opposite effect. IRF7's inhibition of carotid thickening and the expression of VSMC proliferation markers were dependent on the interaction of IRF7 with ATF3 and its downstream target, proliferating cell nuclear antigen. These findings demonstrate that IRF7's modulation of neointima formation and VSMC proliferation in response to carotid injury and platelet-derived growth factor-BB stimulation is dependent on ATF3.

## Protective effects of activating transcription factor 3 against ischemia/reperfusion in the brain

In a study of brain injury after transient focal cerebral ischemia, $ATF3^{-/-}$ mice showed significantly higher infarct volume and worsened neurological function as well as upregulation of neural apoptosis, inflammatory gene expression, and the cellular inflammatory response [33]. In addition, the protective effect of ATF3 was mediated by the downregulation of carboxyl-terminal modulator protein (CTMP), a proapoptotic factor that inhibits the antiapoptotic protein kinase B cascade [34]. Both reporter and chromatin immunoprecipitation assays demonstrated that ATF3 suppressed CTMP transcription by fusing with herpes simplex viral protein vmw65 (VP16), resulting in the binding of ATF3 to the ATF/CREB site and the inhibition of NF-κB binding to the CTMP promoter [34]. ATF3 can be induced in neurons or in microglial cells by the cytokine IL-6 [35]. Furthermore, a study reported that ATF3 was upregulated in the inflamed spinal cord of animals with constriction injury of the sciatic nerve [35] and in the pontine nuclei following demyelination of the pontocerebellar tract. In a patient with Marburg's variant of multiple sclerosis, ATF3 was found in neurons within the pontine nuclei and neocortex [36]. A caveat is that the extent of axonal injury in such cases of demyelination remains unknown. The expression of neuronal injury factors might initially trigger satellite glial cells (SGCs), which play an important role in the mechanisms of articular inflammation and inflammatory pain, whereas ATF3 might show an inverse correlation with inflammation involved in SGC activation or seizure [37]. ATF3 exhibits neuroprotective effects by inhibiting inflammation-induced neuron injury, and the tripeptide glycine–proline–glutamate analogue NNZ-2566 (Neuren Pharmaceuticals, Port Melbourne, Australia) demonstrated neuroprotective effects by increasing both the mRNA and protein levels of ATF3 [38].

In murine neocortical neurons previously cultured under ischemic conditions for 2 h, the transient upregulation of both Atf3 and ATF3 expression was similarly found during subsequent culture for 2–24 h under normoxia. The lentiviral overexpression of ATF3 ameliorated the neurotoxicity of glutamate in cultured murine neurons, in addition to significantly inhibiting both fluo-3 and rhodamine-2 fluorescence increases induced by N-methyl-D-aspartate [39].

## Conclusions and perspectives

In a study of multiorgan failure, which is associated with I/R or inflammation, ATF3 was identified as a rapidly induced transcription factor of stress stimuli, and ATF3 strongly repressed the transcription of inflammatory cytokines, including IL-6, TNF-α, and interferon-γ [18,22]. Moreover, increasing evidence has clarified the mechanisms through which ATF3 has antiapoptotic and anti-inflammatory effects in various organs with induced dysfunction [Figure 1]. ATF3 can reduce inflammation- or I/R-induced injury by ROS in multiple organs. Recently, our research team has focused on the role of ATF3 in metabolism dysfunction syndromes such as obesity and diabetes. Accumulating evidence suggests that obesity may be considered a chronic low-grade inflammatory disease and a metabolic disease. The unbalanced production of pro- and anti-inflammatory adipocytokines critically contributes to obesity-induced insulin resistance [40]. A previous study showed that ATF3 expression was increased in the abdominal subcutaneous adipose tissue of obese mice. Kim *et al*. indicated that ATF3 functions as a negative regulator of adiponectin gene expression, which may play critical roles in downregulating adiponectin expression in obesity and type 2 diabetes [41]. ATF3 also represses the C/EBPα gene, resulting in the inhibition of adipocyte differentiation [42]. Furthermore, our previous studies have revealed that ATF3 can regulate adipocytes *in vitro* and have confirmed that it can modulate high-fat diet-induced adipocyte hypertrophy and lipid metabolism in mice (*in vivo*). Therefore, we must extend study beyond the role of ATF3 in I/R to its role in inflammation-induced metabolic syndrome.

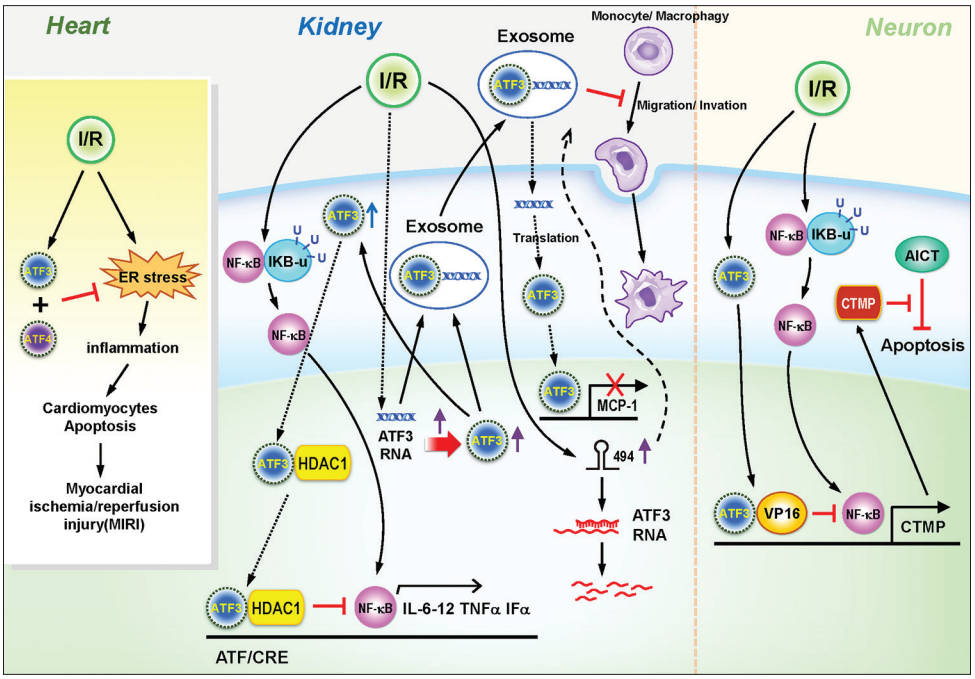


**Figure 1:** Schematic representation of the signal transduction pathway of ATF3 protecting against I/R-induced inflammation, apoptosis, or myocardial injury in various organs. ATF3: activating transcription factor 3, CRE: ATF/cyclic AMP response element, CREB: ATF/cAMP response element-binding protein, CTMP: carboxyl-terminal modulator protein, ER: endoplasmic reticulum, HDAC: histone deacetylase, MCP-1: monocyte chemotactic protein-1, NF-κB: nuclear factor kappa-light-chain-enhancer of activated B-cells, TNF-α: tumor necrosis factor-α, VP16: herpes simplex viral protein vmw65

Knowledge of the single-molecule inducer of ATF3 is limited. Ultimately, from a therapeutic standpoint, we have much to anticipate regarding the use of a screening platform to identify the ATF3 inducer as well as the clinical application of ATF3 in anti-inflammatory therapies for I/R- or inflammation-induced multiorgan failure and chronic inflammation-induced metabolic disorder.


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## Conflicts of interest

There are no conflicts of interest.

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