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Targeting BNIP3 in inflammation-mediated heart failure: a novel concept in heart failure therapy

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Abstract Myocardial injury activates inflammatory mediators and provokes the integration of BCL-2/adenovirus E1B 19KD interacting protein 3 (BNIP3) into mitochondrial membranes. Translocation of BNIP3 to mitochondria inexorably causes mitochondrial fragmentation. Heart failure (HF) epitomizes the life-threatening phase of BNIP3-induced mitochondrial dysfunction and cardiomyocyte death. Available data suggest that inflammatory mediators play a key role in cardiac cell demise and have been implicated in the pathogenesis of HF syndrome. In the present study, we reviewed the changes in BNIP3 protein expression levels during inflammatory response and postulated its role in inflammation-mediated HF. We also identified inflammatory mediators' response such as stimulation of TNF-α and NO as potent inducer of BNIP3. Previous studies suggest that the pro-apoptotic protein has a common regulator with IL-1β and induces IL-6-stimulated cardiac hypertrophy. These findings corroborate our contention that interventions designed to functionally modulate BNIP3 activity during inflammatory-mediated HF may prove beneficial in preventing HF. Such a revelation will open new avenue for further research to unravel a novel therapeutic strategy in HF diseases. Moreover, understanding of the relationship between BNIP3 and inflammatory mediators in HF pathologies will not only contribute to the discovery of drugs that can inhibit inflammation-mediated heart diseases, but also enhance the current knowledge on the key role BNIP3 plays during inflammation.

Keywords BNIP3 · Heart failure · Inflammation · Endoplasmic reticulum calcium

Introduction

Heart failure is a chronic disease characterized by a weakened heart and inability of the heart to supply sufficient amount of blood to meet the perfusion and metabolic needs of the body and to match the demands of organs and tissues for blood and oxygen. The increasing disease burden, continuous hospitalization, and strain on healthcare system despite significant advances of standard therapies (such as β-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, aldosterone receptor antagonists) and synchronizing therapies have renewed the focus of researchers to maximize myocardial salvage by developing new therapeutic targets based on other abnormal molecular and cellular mechanisms involved in the etiology of this syndrome [1–3]. Recent studies have focused on therapy based on regulating inflammation-associated death of cardiomyocytes [4]. A combination of these approaches may provide the best strategies to treat patients at risk of heart diseases. The role of inflammation in the development and progression of HF has been well explicated [5]. In addition, current studies have demonstrated the risk of inflammation in cardiovascular events and hospitalization for deteriorating HF

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increases with the increased levels of inflammatory agents such as CRP, NO, TNF-α, IL-1β, and IL-6 [6–8]. Inhibition of this process would confer effective treatment for HF diseases. Features leading to HF; increased oxidative stress, myocardial injury, increased nitric oxide (NO) levels and inflammatory activities are observed in both the inflammatory agents and BNIP3-mediated cardiac failure [6, 9]. To identify the target of TNF-α-mediated cell loss after a failed clinical trial using TNF-α antagonist, Kim et al. [10] reported that BNIP3 is the therapeutic target candidate for pathological conditions induced by TNF-α. Moreover, studies have associated increase in the expression of BNIP3 with TNF-α and further suggest that TNF-α up-regulates BNIP3 expression [11]. This association is mediated by nitric oxide (NO, an inflammatory mediator by extension) and is inhibited by nitric oxide synthase inhibitor N5-(methylamidino)-L-ornithine acetate (anti-inflammatory agent) [12]. In light of this, Yook et al. [13] postulated that NO is a potent inducer of BNIP3 unraveling the association between BNIP3 and inflammation.

To date, drug discovery for cardiovascular disease therapy targeting BNIP3 largely remains unexplored despite the ongoing research on the role BNIP3 plays in cardiac pathologies. In this review, we surmised that inhibition of BNIP3 does not only contribute to cardioprotection, but could also attenuate the detrimental effects of inflammatory response during myocardial injury.

Causal association between BNIP3 and heart failure

The role for BNIP3 in cardiac myocyte cell death has been confirmed in vivo; in mice subjected to ischemia–reperfusion, BNIP3 deficiency limits post-myocardial infarct-induced ventricular remodeling by reducing peri-infarct apoptosis [14]. Contrariwise, high-level expression of BNIP3 in the heart significantly increases the frequency of apoptotic cells and causes cardiomyopathy [15]. Furthermore, overexpression of BNIP3 in a model rat induces myocardial apoptosis even in the absence of subsequent stress and ultimately results in cardiac hypertrophy, diastolic dysfunction, diminished systolic performance, and contractile dysfunction [14, 16]. Meanwhile, expression of the dominant negative form of BNIP3 (BNIP3ΔTM) represses cardiac myocyte loss and prevents ischemic injury-mediated heart failure [17–19]. Notwithstanding, up-regulation of BNIP3 contributes to apoptosis-induced cardiac hypertrophy during ischemia [20]. This suggests a direct involvement of BNIP3 in heart failure and supports our assertion that BNIP3 up-regulation is the unique pathway for ischemic-induced cardiac dysfunction.

Moreover, elevated BNIP3 levels further down-regulated SERCA2a to decrease diastolic and systolic function and contributed to cardiac remodeling in a failing heart [21]. Additionally, up-regulation of BNIP3 has been observed in coronary artery disease (CAD) cases [22, 23] further strengthening our contention that targeting BNIP3 in heart failure is integral for cardiac function.

Increased expression of BNIP3 in heart failure prompted researchers to test the effects of BNIP3 manipulation in cardiac cells [21]. In the study, a significant decrease in left ventricular volumes with improvement in left ventricular diastolic and systolic function in a BNIP3-knockdown rat model of pressure overload of a failing heart was discovered [24]. Additional discovery was that BNIP3 knockdown could attenuate mitochondrial fragmentation and leads to restoration of mitochondrial morphology and integrity. Significant decrease in endoplasmic reticulum stress and mitochondrial apoptotic markers in BNIP3 knockdown are also reported [25]. In contrast, increased BNIP3 expression decreases myocardial diastolic and systolic function and contributes to the major remodeling process.

Autophagic adaptive response following BNIP3 expression

Activation of autophagy is one of the most important mechanisms involved in cardiac function by inhibiting mitochondrial dysfunction [26–29]. Cardiac myocytes demonstrate ability to stimulate autophagy to protect cardiac function during BNIP3 overexpression as adaptive response mechanism to remove the damaged mitochondria. This confers salutary action on cardiac function by preventing the deleterious effect of BNIP3 in a process similar to inflammation-induced autophagy [15, 30, 31]. Therefore, activation of autophagy in response to BNIP3 expression is vital for mitochondrial function as well as cardioprotection. For example, to confer anti-inflammatory and cell survival, NF-κB mediates the inhibition of both TNF-α and BNIP3-dependent autophagy and apoptosis suggesting the implication of autophagic activity during BNIP3 expression [32, 33].

BNIP3-associated mitochondrial dysfunction is deleterious to cardiac function

Heart failure is associated with alterations in gene availability, substrate oxidation, mitochondrial ATP production, and a decreased mitochondrial biogenesis and function [34]. A revealing report by Montaigne et al. [35] suggests the biological effects of most therapeutic molecules converge to mitochondria as a critical target to elicit a wide range of adverse effects on heart function. This demonstrates that energy deficit plays a significant role in the development of cardiac dysfunction. Of note, the heart has

no excess capacity for energy production during overutilization of energy. ATP is needed to sustain the excitation–contraction coupling and must continuously be available to support an optimal myocardial performance in both systolic and diastolic periods. Ninety percent of this energy is generated by mitochondrial oxidative phosphorylation. For this reason, hemodynamic markers of severity in heart failure are associated with an increase in cardiac mitochondrial oxidative capacity [27, 34, 36].

BNIP3 expression has been implicated in changes in the mitochondrial morphology of cardiac myocytes and in several heart diseases [19, 37–40]. Fragmentation of the mitochondrial network in response to apoptotic stimuli mediated by BNIP3 is commonly observed in cardiac myocytes. Therefore, integration of BNIP3 into the mitochondria is a key metabolic step for ischemic-induced death of cardiac cells following myocardial injury [13]. In the process of cardiac injury, inflammatory responses including NO and TNF-α activation mediate the stimulation of BNIP3 to promote mitochondrial permeability and in effect, induce mitochondrial dysfunction in cardiomyocytes [14–16]. BNIP3 can activate pro-apoptotic proteins such as BAX and caspases to stimulate permeability pore changes which eventually lead to ER Ca^{2+} depletion and mitochondrial dysfunction by interacting with porin/voltage-dependent anion channel (VDAC/porin) and adenine nucleotide transporter (ANT) [17–19]. Ultimately, BNIP3-induced mitochondrial dysfunction causes the transition of the left ventricles from compensatory hypertrophy to heart failure [26, 41, 42].

Role of inflammation in heart failure

The treatment of heart failure has remarkably transformed, and the history of its management is a reflection of our understanding of its pathogenesis. During the last three decades, pharmacological treatment has evolved from therapy based on the cardiac remodeling process and hemodynamic parameters to neuroendocrine systems. The use of standard therapies such as β-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, and aldosterone receptor antagonists is aimed at relieving edema and improving hemodynamics, remodeling process, and cardiac load. However, the use of these therapies is somewhat deleterious on-long-term prognosis. Therefore, there are still unmet vital medical strategies to ameliorate cardiovascular diseases. In recent times, treatment aimed at targeting inflammatory mediators is a promising novel approach to cardioprotection in CHF patients. Clinicians need to identify the combination of these optimal therapies for each patient to obtain effective management of this syndrome.

It is now understood that primary loss of cardiac myocytes is due to myocardial injury and the consequent stimulation of inflammatory response. The mechanism through which inflammation causes heart failure is an ongoing topic of research. Inflammation response leads to heart failure through a complex of clinical progression which results in impairment of cardiac structure and function. Hence, the activation of the plasma concentrations of pro-inflammatory mediators in myocardial injury and acute myocardial infarction may characterize cardiac failure. Positive correlation between inflammatory mediators and chronic HF has been largely reported [7, 43].

Role of TNF-α in heart failure

A number of deleterious effects seem to be associated with increased TNF-α production in chronic heart failure (CHF). TNF-α reportedly causes negative inotropic action and a disturbance of β-adrenergic receptor sensitivity via the inducible form of nitric oxide synthase (iNOs) system [44]. Elevated TNF-α levels also correlated with left atrial dysfunction and the progression of left ventricular diastolic and systolic dysfunction, left ventricular remodeling, and increased cardiac myocyte apoptosis [45]. TNF-α stimulates a cascade of events which lead to the recruitment of adaptor proteins and the activation of caspase-8. Activated caspase-8 starts a mitochondria-independent caspase cascade directly relaying on the activation of caspase-3. Caspase-8 may also cleave and hyperactivate the pro-apoptotic Bid molecule which eventually translocates to the mitochondria and activates the mitochondrial death pathway. Due to the reported detrimental effect of TNF-α, drugs that antagonize the effect of TNF-α are expected to provide beneficial effect to cardiac function. On the contrary, clinical studies conducted to investigate the therapeutic value of infliximab (TNF-α antagonist) recorded no significant improvement of heart failure [8]. What these controversies tell us is that activation of TNF-α occurs through a process where other pro-inflammatory agents are also stimulated including the activation of BNIP3.

Role of IL-6 in heart failure

Activation of IL-6 (a pro-inflammatory cytokine) can lead to myocyte hypertrophy, myocardial dysfunction, impaired left atrial function, advanced left ventricular diastolic and systolic dysfunction, and muscle wasting which have been shown in the progression of CHF patients [46]. Its predictive value in HF progression became more apparent after the discovery that IL-6 level is a risk factor to HF in the elderly. Numerous studies from American Heart Association [47] and European Journal of Heart Failure [48] have all implicated IL-6 in HF pathogenesis and

suggested the pro-inflammatory agent as a prognostic marker in the pathophysiology of cardiovascular events.

Role of CRP in heart failure

Increased levels of CRP, an inflammatory marker have also been found to correlate with HF disease progression. CRP can induce myocardial impairment through complement activation, endothelial dysfunction, and impairment of left ventricular dysfunction [43]. Clinical studies from 4691 subjects found that the relative risk of hospital admission for HF was twofold in those whose CRP levels were above 3 mg/L [7]. Various studies have shown its production in the pathophysiology of cardiovascular diseases, suggesting that CRP is not just a biomarker for inflammation, but may also play a vital role in the development of HF. Preponderance of evidence indicates that the acute phase protein is involved in inflammatory-mediated events including atherosclerosis and myocardial infarction [49]. CRP is also a risk factor for HF with elevated levels reported in serum of smokers, obese, and hypertensive patients. Thus, CRP assessment can be used at the discretion of physicians as a prognostic tool for cardiovascular events and inflammatory-mediated conditions (Fig. 1).

Role of IL-1β in heart failure

IL-1β is an important pro-inflammatory cytokine involved in myocardial apoptosis, hypertrophy, arrhythmogenesis, idiopathic dilated cardiomyopathy, and impairment of myocardial contractility [6]. Activation of iNOS (an inducer of BNIP3) triggers the release of IL-1β, and its aforementioned effects are synergistic with that of TNF-α. IL-1β stimulates inducible nitric oxide synthase, which increases the formation of reactive oxygen species and reactive nitrogen species (e.g., nitrotyrosine) [50]. This leads to the activation of BNIP3 and consequently results in heart failure as shown in Fig. 2 [51]

Association between BNIP3 and inflammation

The missing link between BNIP3 and myocardial inflammation is becoming more apparent with increasing number of evidence that BNIP3 mediates cell death caused by inflammatory cytokines [10]. Crosstalk between inflammation and BNIP3-mediated heart failure is rarely discussed even though HF is always the result of some underlying processes including inflammation and BNIP3 signaling pathways. Increased levels of pro-inflammatory cytokines, IL-1β, IL-6, and TNF-α are observed in patients with HF and play crucial role in the development of cardiac myocyte apoptosis, cardiac hypertrophy, myocardial dysfunction, and cardiac remodeling. These candidates have potential pathogenetic impact on the heart. Thus, their association with BNIP3 is important for the assessment of systemic inflammatory response syndrome such as cardiomyopathy and heart failure diseases. Therefore, it is imperative to unravel this association and identify BNIP3 as a target candidate for the management of inflammation-mediated heart failure. It can be inferred from previous studies that during hypoxia or cardiac stress through a cascade of inflammatory responses involving the production of TNF-α, IL-1β, and NO, BNIP3 is stimulated to mediate cardiac dysfunction. Available data suggest the causal association between pro-inflammatory cytokines and BNIP3 activation. Inflammatory mediators including TNF-α and NO activate BNIP3 during stress or injury which subsequently depletes endoplasmic reticulum Ca^{2+} and induce mitochondrial dysfunction and apoptosis. The stimulation of BNIP3 during inflammatory response could lead to heart failure and may reflect the process of how the inflammatory process and BNIP3 pathways are linked in the pathogenesis of heart failure. This may be an integral cell death pathway through which inflammation leads to myocardial dysfunction [38, 52–55].

Several strategies to counterbalance different aspects of the inflammatory response such as targeting pro-inflammatory cytokines, nitric oxide, reactive oxygen species, and NF-κB are considered in the management of a failing heart. This study reveals that during inflammation response, BNIP3 expression is altered in human heart failure and recommends the inhibition of BNIP3 during inflammation-mediated heart failure as a new therapeutic target.

It is important to note that the influence of NF-κB on cell survival could be protective or destructive, depending on cell types, developmental stages of cells, and pathological conditions. Moreover, IκB kinase (IKK) NF-κB is a negative regulator of both IL-1β secretion and BNIP3 activation as revealed by Lawrence [56] and Trocoli et al. [57]. Moreover, BNIP3 and IL-1β are both regulated by IFN-γ, suggesting that inflammation is an inducible factor that initiates BNIP3 activation during the development and progression of heart failure [21, 58, 59]. Furthermore, while IL-6 plasma levels are elevated and associated with an impaired prognosis in advanced heart failure, recent research spotlight on the link between the pro-apoptotic protein and inflammatory cytokines reveals how BNIP3 increases the expression of IL-6 following myocardial injury. Weng et al. [60] have shown that BNIP3 induces IL-6 in H9c2 cardiomyoblast cells which plays key role in the development of heart failure. Activated serum IL-6 levels correlate with reduced contractility, elevated preload, elevated heart rate, and reduced afterload in patients with impaired left ventricular function [7]. BNIP3-induced

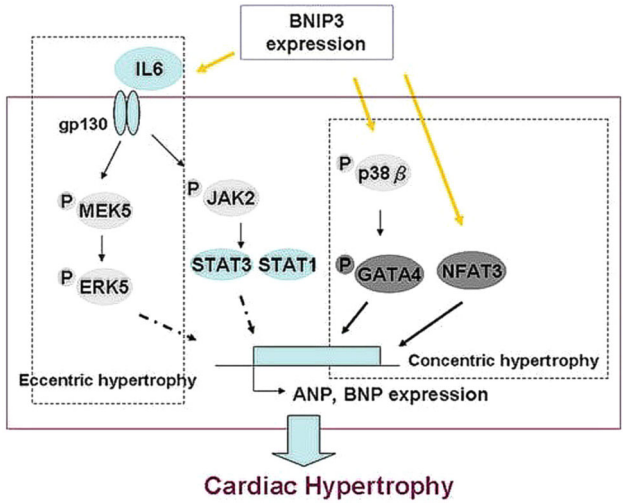

Fig. 1 BNIP3 induces IL-6 to cause cardiac hypertrophy [1]

release of IL-6 triggers gp130 dimerizing leading to phosphorylation and activation of JAK2 and consequent recruitment of STAT 3. Activated STAT 3 forms homodimer or heterodimer with STAT 1 to transcribe the target gene. MEK5-ERK5 signaling is also induced by IL-6. Thus, overexpression of BNIP3 activates IL6-MEK5-ERK5, IL6-JAK2-STAT1/3, calcineurin/NFAT3, and p38β MAPK as shown in Fig. 1 [60]. Interestingly, phosphorylated STAT 1/3, ERK5, and MEK5-ERK5 have all been implicated in dilated cardiomyopathy, cardiac hypertrophy, and HF. Thus, major pathways through which BNIP3 leads to cardiac cell demise and heart failure act through pro-inflammatory processes.

Induction of inducible nitric oxide synthase is an essential part of TNF-α-induced apoptosis. Notably, nitric oxide has been reported to be a potent inducer of BNIP3 suggesting a crosstalk between inflammatory mediators and BNIP3. Experimental data have suggested an increased NO synthesis in a failing myocytes and the involvement of BNIP3 in NO-induced left ventricular systolic and diastolic dysfunction indicating the participation of BNIP3 in inflammation-stimulated myocardial damage [61].

BNIP3 is the target therapeutic candidate for TNF-α mediated heart failure

The mediation of TNF-α-induced cardiomyocyte loss and the activation of interleukin-6 levels (that leads to cardiac hypertrophy) by BNIP3 have led to the appreciation of the

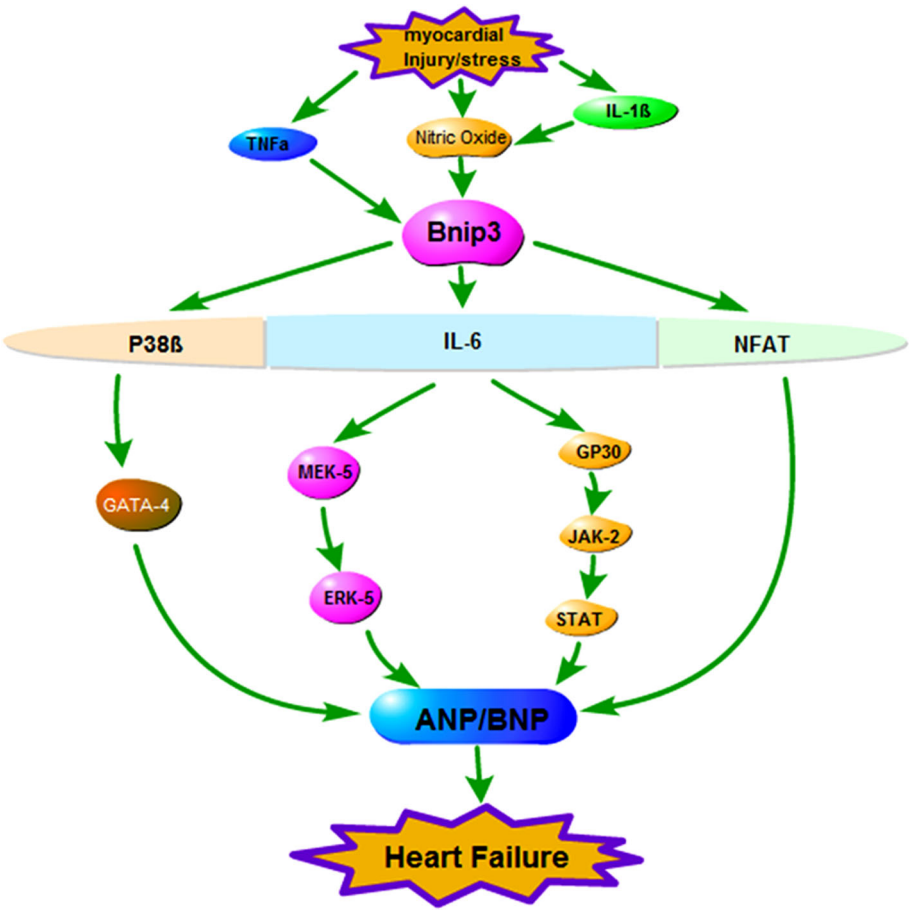

Fig. 2 Mechanism of BNIP3-induced cell death

understanding of the crosstalk between BNIP3 and pro-inflammatory cytokines in the pathogenesis of this syndrome [60]. Consistent with the role for BNIP3-induced heart failure, the transgenic mice with chronic overexpression of TNF-α resulted in the development of myocarditis, ventricular hypertrophy, dilated cardiac myopathy, and diminished ejection fraction. Elevated TNF-α level found in heart failure patients and cardiac-specific overexpression of TNF-α results in dilated cardiomyopathy. Available data suggest that decreased anti-apoptotic effect of NF-κB enhanced apoptotic activity of TNF-α and BNIP3 during heart failure [62]. Furthermore, treatment with a soluble TNF-α receptor lowered TNF-α in patients and improved left ventricular function. Kim et al. [10] reported that BNIP3 mediates the cell demise caused by TNF-α and that inhibiting BNIP3 hampered the TNF-α-induced lethalities. During inflammatory response, TNF-α increases the expression level of BNIP3 which is mediated by nitric oxide. This effect is significantly inhibited by nitric oxide synthase inhibitor N5-(methylamidino)-L-ornithine acetate. To corroborate this assertion, inhibition of nitric oxide, herein mediator of BNIP3 expression is reported to attenuate myocardial depression induced by TNF-α and IL-1β. Interestingly, a number of evidence point out that BNIP3-mediated cell loss resembles TNF-α-induced cell death unraveling the crosstalk between BNIP3 and inflammatory cytokines. Recent reports suggest that ablating BNIP3 can restrain TNF-α-induced cardiomyocytes apoptosis and post-infarction remodeling [10]. TNF-α is also a pathological BNIP3 inducer, which might be a potential therapeutic target for heart damage prevention. Thus, considering BNIP3 as an important target candidate is a worthwhile therapeutic approach which would allow development of new targets for therapeutic intervention and to reduce inflammation-induced heart failure.

Epigenetic regulation of BNIP3 in cardiomyocytes

E2F transcription factor-1 (E2F-1) transcriptional activation of BNIP3 is lethal to ventricular myocytes [63, 64]. NF-κB-HDAC-dependent mechanism displaces the E2F-1 and is a survival mechanism in ventricular myocytes [64–66]. Functional loss of NF-κB signaling in cardiac myocytes increases cardiomyocyte susceptibility to TNF-α-induced apoptosis which is similar to findings in cardiomyocytes where inhibition of NF-κB enhances BNIP3-induced apoptosis [67].

Epigenetic regulation of BNIP3 has been shown to play a crucial role in the progression of various types of diseases such as cancer and cardiovascular disorders [30, 68–70]. On the subject of this, the previous studies have explicated the mechanism by which BNIP3 can be epigenetically regulated and evaluated its clinical importance in the management of BNIP3-mediated diseases [30, 64, 68]. In pancreatic cancer cells, down-regulation or silencing of BNIP3 by hypermethylation caused resistance to hypoxia-induced cell death [16, 30, 70]. DNA methylation of BNIP3 and histone deacetylation in cardiac myocytes resulted in the silencing or reduced expression of BNIP3 and influenced cell survival in hypoxic conditions [30, 66]. Conversely, hypomethylation of BNIP3 causes the up-regulation of the protein's expression level and contributes to the development of coronary heart diseases which profoundly provokes cardiac dysfunction [68, 71]. In cardiac infarction, loss of BNIP3 expression has been shown to reduce the number of damaged cardiomyocytes and reduce infarct size [16]. Due to the pathological roles of BNIP3 in inducing cell death that leads to the decline of cardiac performance, we postulate that tightly regulating molecular signaling pathways by epigenetically silencing the expression of BNIP3 will be a potential groundbreaking target for therapeutic benefit. Notwithstanding, since epigenetically regulating BNIP3 leads to cardiomyocytes survival, we recommend further clinicopathological analysis to shed more light on the regulatory function of NF-κB to clarify the controversies between its pro-apoptotic (and/or anti-inflammatory) and apoptotic activities (and/or inflammatory) following cardiomyopathy, diastolic dysfunction, systolic dysfunction, and cardiac hypertrophy in a failing heart. These could have profound impact in obtaining clinically relevant target necessary for epigenetic drug discovery and to bring forth novel therapeutic strategies needed for the management of cardiac dysfunction.

Concluding remarks

This review examined the possible activation of BNIP3 in the context of inflammation-mediated etiology and progression of heart failure. We provided accumulated evidence in both human and animal models, suggesting that BNIP3 is a significant contributor to the pathogenesis of inflammation-induced heart failure pathologies. Elevated levels of inflammatory mediators in a failing heart have been reported. Intriguingly, BNIP3 has been found to be induced by TNF-α and NO. The pro-apoptotic protein mediates the detrimental effects of the inflammatory agents and also induces IL-6 which results in the progression of heart diseases. It is widely reported that ablation of BNIP3 significantly improves cardiac function. The possible mechanism through which BNIP3 leads to HF may be associated with its role in inflammation and the depletion of ER Ca^{2+} and the consequent activation of the multi-domain pro-apoptotic protein, BAK, and BAX by BNIP3 to

trigger cytochrome C release. Cytochrome C stimulates caspases to induce mitochondrial dysfunction and apoptosis. Research focus on inhibiting BNIP3 levels during inflammation will be a crucial process of protecting the myocardium from injurious effect of inflammatory responses. These interventions to clinically manage heart failure may represent a noteworthy therapeutic approach for novel treatment options to preserve cardiac function and to discover more effective, specific, and safer therapies.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Human and animals rights This article does not contain any studies with human participants or animals performed by any of the authors.

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