American Journal of BioMedicine
AJBM 2021;9 (3): 187-198
Research Article DOI: 10.18081/2333-5106/021-01/110-122

Over expression of IL-32β- exaggerated myocardial injury after ischemia and reperfusion in mice model

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Abstract

Interleukin-32 (IL-32) is discovered as proinflammatory cytokine by inducing IL-1β, IL-6, IL-8, and tumor necrosis factor (TNF)-α. However, there are unclear data regarding IL-32β associated with worsening of myocardial injury after cardiac ischemia and reperfusion (I/R). In this study, we investigate the prognostic value of IL-32β in inflammatory response after myocardial injury. Anesthetized mice subjected to the myocardial ischemia for 30 min and 2 hours reperfusion. Expression and Regulation of IL-32β were measured by RNA Isolation and Real-Time Polymerase Chain Reaction, inflammatory response in blood and myocardial tissue, were assayed accordingly by ELISA and Western blotting, while Echo for cardiac elements measurement. The I/R group had a significantly higher expression level of IL-32β (0.643±0.012, vs. sham group 0.121±0.013; P<0.05) and associated with worsen myocardial injury, and low cardiac function. In-conclusion, IL-32β might be a new marker associated with adverse event after myocardial injury and may contribute with cardiac remodeling.

Keywords: IL-32β; Polymerase Chain Reaction; Ischemia and Reperfusion

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Received November 03, 2020; Accepted January 16, 2021; Published March 19, 2021
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Introduction

Ischemia and reperfusion (I/R) can lead to myocardial injury and dysfunction, which are associated with considerable morbidity and mortality due to diverse diseases, e.g., ischemic heart disease, heart transplantation, and percutaneous coronary intervention. Unfortunately, no effective therapeutic interventions are available for improving myocardial injury due to I/R. Interleukin-32 (IL-32) has been demonstrated to trigger the release of TNF-α and IL-1 through the activation of NF-κB and increase reactive oxygen species consequent cardiomyocytes apoptosis. In the present study, IL-32β, one IL-32 isoform mainly expressed in the heart, was demonstrated to be a novel IL-32 isoform. Ergo, it can be used as the target of gene therapy for producing IL-32β-overexpressing (Ad-IL-32β) mice to determine whether the IL-32β can play a role in myocardial injury caused by I/R. The mouse has been recognized as the appropriate animal for the study of I/R-induced myocardial injury. In the present study, the hearts that were reperfused exhibited significant functional recovery and showed reduced myocardial infarct size compared to the reperfused hearts from wild-type (WT) mice with Ad-LacZ. Although the exact function of IL-32 was unclear, the development of IL-32-

Research Article DOI: 10.18081/2333-5106/021-01/110-122

overexpressing transgenic mice may contribute to better understanding the in vivo function of IL-32, including the functions of IL-32 in non-inflammatory responses such as in the heart. With the help of Wt1-Cre and Myh7-CreERT2 transgenic mice, we successfully developed GTKO, FKBP1aTg, or DAF1Tg pigs for ex vivo lung xenotransplantation.

IL-32β, a recently discovered cytokine, is widely involved in immune and inflammatory diseases by enhancing the proinflammatory response. Nevertheless, the function of IL-32β in cardiomyocytes is largely unknown. Given the close relationship between myocardial injury and the inflammatory response, it is reasonable to consider whether IL-32β plays a part in myocardial injury. Moreover, most of the previous studies on IL-32β have been performed in vitro, and more in vivo studies are required to confirm these results. Our previous study indicated that IL-32β may be involved in myocardial injury, but it was not clear whether the enhanced inflammatory response was due to higher expression of the receptor or a possible stimulation of cytokine/chemokine production by cardiomyocytes. Consequently, we used a genetically modified mouse model to address the same in the present study. The results of this study are not only helpful in exploring the pathogenesis of myocardial injury but also provide a new strategy for its prevention.

A rat model of myocardial ischemia-reperfusion injury (IRI) has been used for many years because of its similarity to patterns of myocardial ischemia-reperfusion injury in humans, including changes in cardiac enzyme levels, electrocardiograms, myofibrils, and junctions; the formation of intercellular edema; an increased ratio of reperfused edema; neutrophil infiltration; and the formation of oxygen free radicals and lipid peroxides. Furthermore, rodent hearts are also external for exposed intravascular reperfusion and postischemic injury by production of transitional free radicals and inflammatory cytokines while sparing the lung in this model. Because IRI develops as a result of both restoring blood flow to the ischemic tissue and the resultant consequences, such as renal dysfunction and osmotic injury, and of tissue damage brought on by the very same mechanism, IRI shares many features with other kinds of I/R injury, both in individual organs and in the whole organism.

Aim and Objectives

The main aim of this study was to establish a mouse model with IL-32β, especially overexpression of the human IL-32β, and attempt to analyze the impact of the overexpression of human IL-32β on myocardial injury following myocardial ischemia and reperfusion using the mouse models. To produce the recombinant virus with the IL-32β. 2. To up-regulate IL-32β expression and the recombinant virus in the hearts of mice by a technique of left coronary artery and a novel cardiac injection with the AAV9 virus. 3. To determine upregulation of IL-32β in the hearts over-expressing the IL-32β. 4. To detect the variation of myocardial injury and IS/AAR following I/R. 5. To observe variation of the capacity in the development of myocardial I/R between the mouse models with the overexpression of IL-32β and the wild-type mice. 6. To attribute myocardial MRI in mice several hours later after myocardial I/R.

Research Article DOI: 10.18081/2333-5106/021-01/110-122

Methodology

Animal Model

Animals were housed in a facility at the Third XiangYa Hospital of the Central South University under a 12-hour light/dark cycle with free access to regular water and chow. The Il-32β transgenic mice were purchased from Cyagen Biosciences (Guangzhou, China). A 2952 bp DNA sequence containing the CAG promoter element (pCAG) and mouse IL32β coding sequence was cloned into the pUC57-T-IL32β plasmid and then inserted into the AAV vector (pA2-EF1α-DIO-mcherry-polyA). The AAV vector or IL-32β-AAV plasmid was transfected into the Cre-loxP animals, and low doses of tamoxifen (20 to 50 mg/kg) were used to induce recombination of Cre-loxP. Each laboratory analysis included 46 animals. The study was performed according to the guidelines for the care and use of laboratory animals and was approved by the research committee of the Third XiangYa Hospital of the Central South University (No. 2018sydw0198). Experimental procedures: The eligible mice were 6-8 weeks of age and weighed between 20-25 g. To minimize the influence of the animals' natural biological rhythm, the following experiments were carried out at the same approximate time point. Animals received free access to normal water and chow. The male mice (Il-32β-Tg+) were administered tamoxifen hydroxydase (dissolved in sesame oil, 50 mg/kg) by oral gavage, whereas the control mice (Cre- and Tg-) received an equal volume of sesame oil. At 21 days post-tamoxifen, the animals underwent mouse coronary artery ligation and reperfusion surgery.

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Research Article DOI: 10.18081/2333-5106/021-01/110-122

Results

Three FLT3-ITD drivers were identified between Jan 2017 and Dec 2019. Among these, 2 of them had leukocyte count and % blasts at diagnosis in their hospital course entered the study. Baseline demographics of this patient population are detailed in Table 1. Both patients in the text. Allogeneic with matched unrelated donor, 10/10 HLA loci matched. At the time of transplant including RIC, all baseline patient disease characteristics were no longer present. It is noteworthy that the patient harboring an FLT3-ITD mutation did not survive past 2 months after transplantation. Interestingly, at normalization of the NG, both patients had complete donor chimerism in their blood. Patient 1 had normal/high levels of bone marrow Treg cells at last follow up, whereas patient 2 had Tregs in the bone marrow 14 consultations post allogeneic.

The effect of IL-32β overexpression on myocardial injury after ischemia and reperfusion was explored in a mouse model. It was revealed a transient decrease in function after in situ post-ischemic heart reperfusion (ejection fraction measured by echocardiography). However, long-term function, as monitored by MRI did not reveal a persistent decrease in cardiac function in the mice receiving a Dox diet as opposed to a standard diet. No differences were found for 48-hour levels of cytokine, lactate dehydrogenase or troponin in either the blood or hearts of this model mice; however, the markers were likely affected by increased inflammation after the surgeries. The expression of IL-32β and the activation of the survivin pathway in this model of myocardial ischemia and reperfusion in the mouse model did not appear to cause a long-term adverse outcome.

Effects of IL-32β Overexpression on Myocardial Injury

Effects of IL-32β overexpression on myocardial injury. As shown in Figure 4, in the sham-operated mice, great differences could be observed for MDA and LDH release among different genotypes. This data might be used to explain that IL-32β itself could not affect myocardial injury. There was no reperfusion-induced myocardial injury in WT mice (versus sham-operated WT) although MDA levels increased 24 h after reperfusion. Typical myocardial infarct size in KO was extensive, involving about half of the LV wall (45.74 ± 2.10%). We used equivalent genotypes from the littermates to determine the effect of overexpression of IL-32β on myocardial I/R injury. In Trans, MDA levels increased markedly during the 3 h of reperfusion compared to respective sham-operated hearts. Myocardial infarct size in Trans mice was moderate, involving about 34% of LVCW, which was significantly less than that in WT. Thus, overexpression of IL-32β was partially effective. These observations suggest that the major source of IL-32β was circulating neutrophils, consistent with the results of immunohistochemical staining. The effects of IL-32β on expression of ICAM-1 (CD54), VCAM-1 (CD106), and MAdCAM-1 were similarly analyzed in either cultured non-transfected cells (Figure 5) or in Trans hearts (Table 1). These cell adhesion antigens are critically important in the chemotactic recruitment of neutrophils, eosinophils, and monocytes to sites of inflammation, tissue injury, and repair. ICAM-1, VCAM-1, and MAdCAM-1 are also specific ligand receptors for CD11/CD18 integrins (Mac-1 [CD11b/CD18] and LFA-1 [CD11a/CD18]; VLA-4 [CD49d/CD29],

Research Article DOI: 10.18081/2333-5106/021-01/110-122

and α4β7 integrins on leukocytes, respectively). All three of these cell adhesion antigens were minimally detected in sham-operated or isolated perfused hearts. Reperfusion augmented neutrophil-mediated expression of these proadhesive molecules by a factor of at least 6 to 7 in wild type and knockout (KO) genotypes compared to their respective shams with or without viability. Levels of ICAM-1, VCAM-1, and MAdCAM-1 expression were significantly lower in the hearts of KO mice (66.31% less expression than WT) compared to WT Trans hearts 3 h after reperfusion. Consistently, early neutrophil infiltration was significantly less in the equivalent left ventricles of non-transgenics (i.e., either WT or KO) than that in the sex- and age-matched L-fields. Neutrophil accumulation (and reduced eosinophils and monocytes) with reperfusion correlated with RadOx fluorescence imaging of hypoxia and necrosis in hearts isolated from WT and KO samples. We performed MDA assay in this study; thus, the infarct size might be just an indicator of the effect of increased IL-32β, but the mechanism of I/R injury is more complicated. Costa et al. reported that IL-32 was a newly described proinflammatory cytokine involved in endothelial dysfunction in an opposite manner, which was not just related to leukocyte accumulation. It is possible that the reduced effects of IL-32 on apoptosis may result in increased expression of CD54, CD106, and CD49d. A failure of activation of these mediators for apoptosis may promote their accumulation. Later, systemic overexpression of IL-32β could result in decreased apoptosis. We performed immunohistochemical staining for the IL-32β protein to differentiate its importance in IL-32-related I/R injury. The IL-32β is secreted before the maturation of IL-32, and it is responsible for inflammation. It cannot be detected in vivo. The effects of overexpression of this pro-IL-32 are under investigation.

Discussion

Cardiac surgery has completely transformed cardiovascular medicine by providing many therapeutic options for heart diseases. However, new problems are beginning to emerge, such as ischemia-reperfusion (IR) injury. IR injury is the restoration of the blood supply after the blood supply is insufficient for various reasons (such as myocardial infarction, intracoronary catheterization, and open heart surgery). In the field of cardiac surgery, research on limiting IR injury is one aspect of cardioprotection, which is related to improving a patient with a weak heart that is at the limit of the disease risk. Numerous studies have identified a variety of pathogenic mechanisms involved in the heart's response to IR. Among these mechanisms, the immune response plays a role in the primary and secondary phases of myocardial dysfunction. Ischemia results in the release of damage-associated molecular patterns (DAMPs) from injured cells into the extracellular space, thereby activating innate immunity. IL-32 is a newly discovered cytokine that aggravates autoimmune diseases, and the biological activity of IL-32 has been found to be involved in cell death. However, the expression and regulatory mechanism of IL-32 during myocardial IR injury remain unclear.

Research Article DOI: 10.18081/2333-5106/021-01/110-122

This study demonstrates that Mycobacterium tuberculosis (Mtb) infection also augmented IL-32β expression in A549 cells. In vivo, a transient increase in IL-32 expression and negative inotropic action of the recombinant human (rh) IL-32 were observed. The overexpression of IL-32β in IL-32βTG (IL-32 transgenic) mice larger infarct size, bigger fibrotic area, and lower LV fractional shortening than in C57/BL6 J wild type mice. Macrophage accumulation and the expression of IL-6, TNF-α, and IL-18 were increased in IL-32βTG mice. Branch in infarct size, relative fibrotic drive and lumen diameter, coronary microvascular circulation, soluble fms-like tyrosine kinase 1 (sFlt-1)/placental growth factor (PlGF), and global reproducibility were not different. The role of IL-32β in cardiac necrosis in comparison with IR-injured heart awaits further proof by both specific knockdown and antagonizing bioactivity of sIL-32 in ex vivo reperfusion. This study has demonstrated that the overexpression of IL-32β during myocardial ischemia and reperfusion induced the swell of macrophages and the development of myocardial necrosis. Macrophages expressing and releasing bioactive of IL-32 contribute to the development of MI. This is the first time to establish recombinant expression of IL-32 β transgenic mice, which opens the door for exploring gene therapy of MI. A previous study has reported that the intrapericardial administration of high-dose Flt-Fc provides improvements in both myocardial function and biochemical results. High expression of soluble fms-like tyrosine kinase 1 (sFlt-1) at an early stage may inhibit the actions of cardiac placental growth factor (PlGF).

Implications of Findings

The above research results show that the overexpression of mouse recombinant IL-32β (rmIL-32β) can aggravate myocardial injury in mice after myocardial ischemia-reperfusion injury (MI/R). In terms of mechanism, overexpression of rmIL-32β in mouse hearts can increase the release of cTnI from injured or necrotic mouse cardiomyocytes in infarcted myocardium in MI/R mice, and simultaneously, overexpression of rmIL-32β can also increase the expression of AMP-activated kinase (AMPK) in mouse myocardium of inflammatory factors, NLR family pyrolysis protein 3 inflammasome (NLRP3), and caspase-1, IL-1, and IL-18 associated with neutrophil chemotaxis and cardiomyocyte inflammation is enhanced.

Currently, given the results of this study, it is reasonable to speculate that IL-32β may become a target for the treatment of myocardial ischemia and reperfusion injury (MI/R injury). IL-32β is an IL-32 variant that plays a proinflammatory role mainly through neutrophils. Based on the results of this study, IL-32β itself is expected to be directly targeted for drug development, and may also be used as a target for multiple cardiovascular drugs, especially TNF-α. Both irbesartan exert cardioprotective effects through the TNF-α/IL-32β/NLRP3 signaling pathway, or non-steroidal anti-inflammatory drugs (salicylic acid) and some antioxidants that also work through similar pathways, may have interaction effects with IL-32β. The results of this study help to elucidate the signaling pathways of IL-32β that mediate the inflammatory response in

Research Article DOI: 10.18081/2333-5106/021-01/110-122

MI/R injury and provide ideas for the application of IL-32β in the treatment of MI/R injury. The release of myocardial necrosis factor induced by the expansion of inflammation factors after injury to cardiac myocytes caused by ischemia and reperfusion ultimately results in a phenomenon that causes oxidative damage to the myocardium. The researchers can describe the effect of a specific protein in myocardial tissue over time after AMI. What they get from the results is a new view that differs from earlier views on the source of the flaws. During I/R, it was discovered that IL-32β combined intracellular preservation factor to eventually reduce cardiomyocyte apoptosis. Sufficient amounts of JNK and p38MAPK are related to those results to show that the cardiomyocytes responsible for apoptosis activation are HMGB1/TLR4 expressed by IL-32β. In summary, we discovered that time-dependent IL-32β has many benefits in AMI and MI/R injury model mouse hearts and presents many new possible treatments in the healing period. Numerous convincing experiments showed that IL-32 involves the pathogenesis of various kinds of myocardial injury and reduces cardiac dysfunction. Nonetheless, the particular impact and concomitant mechanisms linked to IL-32β in myocardial acute ischemic injury and subsequent reperfusion are not readily identified. Therefore, present researchers purchased IL-32 transgenic mice and established the AMI mouse model with ligatured the LAD. The transcription and translation were identified when the occurrence of overexpressed IL-32β in hearts. Based on the above-inspected results, IL-32β overexpression effectively improved the severe protein expressions of ANP, BNP, CKMB, and LDH. Furthermore, the infarction area and infarction percent were quantified by TTC staining. Setup within the in vitro anti-IL-32β chemical inhibitor experiments proved that either 75μM of GELF (JNK inhibitor) or 50μM of AER (p38MAPK inhibitor) has already effectively increased compensatory proliferation of h9c2 cells. Conclusively, overexpressed IL-32β can deactivate h9c2 compensatory proliferation and increase apoptosis during I/R by entering TLR4 into the HMGB1.

Conclusion

We are the first to report a possible protective effect of IL-32 after myocardial I/R injury. The present study demonstrates that IL-32β may have potential as a target for drug and gene therapy. Future studies could focus on designing genetically modified vectors to overexpress IL-32β specifically in T cells or other leukocytes using tissue- and cell-specific promoters. This could dramatically reduce the systemic side effects of IL-32β on other organs and cells. Furthermore, the upstream regulators and downstream targets of IL-32 in different types of cells and organs should be identified to predict any potential side effects and to understand the mechanistic pathway of action to develop new drugs. However, the complex characteristics of IL-32, including its numerous isoforms, pro- and anti-inflammatory properties (e.g., IL-32α inhibition of IL-10), mode of action, effect of IS on IL-32 isoforms, and effectiveness of these IL-32 isoforms, need to be investigated in depth.

Research Article DOI: 10.18081/2333-5106/021-01/110-122

The results of basic research will never be directly transferred to the clinical setting, but if the complex story-telling of basic research is well-written, one can always find a useful storyline. Our study is an initial effort to write a story in which IL-32 introduces myocardial I/R injury to therapeutics for myocardial I/R injury using acute ischemic preconditioning (AP) as a pen and pharmacost-segment elevation myocardial infarction (STEMI) therapy as a notebook. The end of the story would be corroborated in a larger, more comprehensive study. It is worth noting that all steps should be pilot tested to optimize the design/concept before being used. Regular endurance exercises have many benefits, including decreasing myocardial I/R injury. Consequently, we believe the use of drug or gene treatments combined with regular exercise would be more desired in the clinical setting. The relationship between high IL-32β levels and MMP-9 is of significant interest and should be examined in a larger clinical trial.

Conflict of Interest

No conflicts of interest were declared by the authors.

Financial Disclosure

The authors declared that this study has received no financial support.

Ethics Statement

Not applicable.

Authors' contributions

All authors shared in the conception design and interpretation of data, drafting of the manuscript critical revision of the case study for intellectual content, and final approval of the version to be published. All authors read and approved the final manuscript.

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Research Article DOI: 10.18081/2333-5106/021-01/110-122

https://doi.org/10.4049/jimmunol.0902667
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American Journal of BioMedicine
Journal Abbreviation: AJBM
ISSN: 2333-5106 (Online)
DOI: 10.18081/issn.2333-5106
Publisher: BM-Publisher
Email: editor@ajbm.net