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Full paper

Upregulated expression of NINJ1, a membrane-rupturing protein, in cardiac tissue in myocardial ischemia/reperfusion (I/R) injury in mouse and rat models

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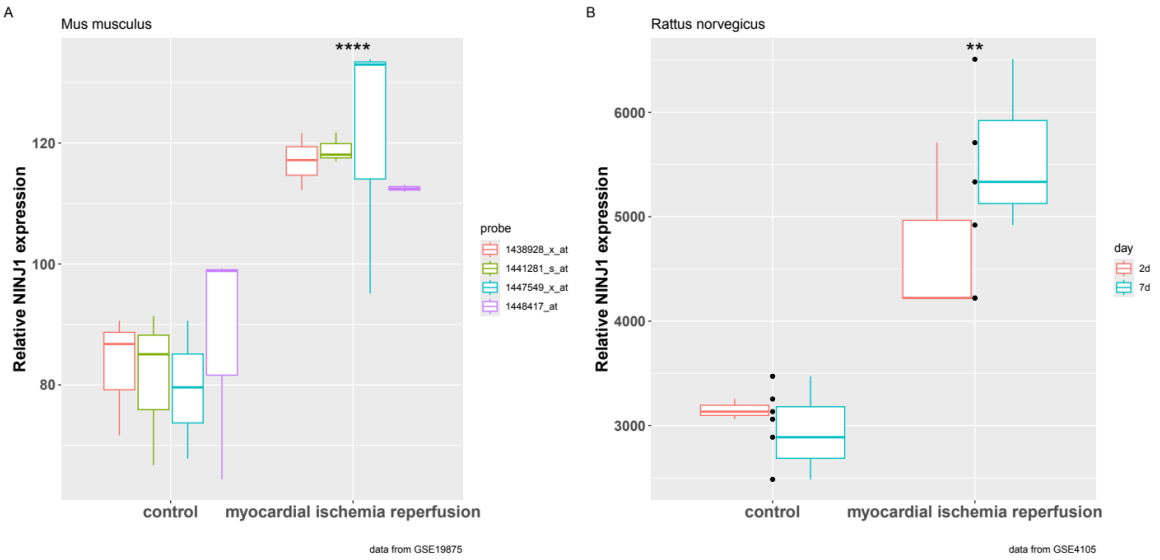
Abstract

Cardiomyocyte death induces irreversible injury during myocardial ischemia/reperfusion (I/R). Multiple regulated cell death programs including ferroptosis, necroptosis, and pyroptosis have been implicated in the pathogenesis of myocardial I/R injury. NINJ1 (Ninjurin-1) mediates plasma membrane rupture and loss of plasma membrane integrity during different lytic cell death mechanisms. Here, we found that, myocardial ischemia/reperfusion significantly increases NINJ1 expression transcriptionally in the heart tissue of both mice and rats. NINJ1 might hypothetically be a more critical therapeutic target in myocardial I/R injury, since it represents a common membrane-rupturing protein during most cell death programs, compared to specific proteins functioning in particular cell death mechanisms. Further mechanistic studies are needed to better understand the involvement of NINJ1 and NINJ1 – mediated plasma membrane rupture in myocardial I/R injury.



Keywords: NINJ1; ischemia; reperfusion; plasma membrane rupture; myocardial injury; isochemia/reperfusion; inflammation; cardiac tissue

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1. Introduction

Myocardial reperfusion therapy is used at the clinic in the treatment of myocardial infarction, to restore coronary artery blood flow and to reduce associated morbidity and mortality in affected patients. Myocardial ischemia–reperfusion (I/R) injury most frequently occurs in coronary artery disease when prompt reperfusion is utilized to salvage the ischemic myocardium and to reduce ischemic damage to cardiomyocytes, i.e. when blood flow is restored to the heart tissue following ischemia-induced damage due to the temporarily interrupted blood flow [1; 2; 3; 4]. Although highly critical for tissue survival and for significantly limiting the infarct size, the restoration of coronary blood flow in the course of reperfusion paradoxically worsens the tissue injury and damage, and leads to additional cell death, resulting in unfavorable clinical outcomes [5]. Cardiomyocyte cell death is the basic pathological factor inducing irreversible injury during myocardial ischemia/reperfusion. Different regulated cell death mechanisms including ferroptosis, necroptosis, and pyroptosis all contribute to the pathological process of myocardial I/R injury [2; 3; 6; 7; 1; 8; 9; 10; 11 12; 13; 14; 15]. These multiple types of regulated cell death can occur simultaneously, interact with each other, and contribute to the complexity of myocardial I/R injury. Since there is an extensive crosstalk and interplay between these programmed cell death mechanisms, accumulating evidence points to the advantage of their combined inhibition to reduce myocardial I/R injury in order to provide cardioprotection in the myocardial tissue [2 3]. However, currently, there is no specific pharmacological treatment against myocardial ischemia-reperfusion injury [16; 17].

The transmembrane protein NINJ1 (Ninjurin-1) mediates plasma membrane rupture (PMR) following its oligomerization, during different lytic cell death mechanisms such as pyroptosis, apoptosis, ferroptosis and parthanatos, but not in necroptosis [18; 19; 20; 21; 22; 23; 24]. NINJ1-mediated plasma membrane rupture is the defining terminal event in the lytic stage of these different forms of programmed cell death [25; 26; 27]. In this active process, NINJ1 oligomers are able to dissolve membranes and/or assemble large pores, leading to the release of large pro-inflammatory molecules (DAMPs such as LDH and HMGB1) to the extracellular space, promoting inflammation and immune response [28]. In other words, most lytic cell death programs (with the exception of necroptosis) culminates in NINJ1-mediated plasma membrane rupture, and NINJ1 is the common executioner of plasma membrane rupture downstream of different regulated cell death mechanisms, resulting in the increased release of large intracellular molecules (cellular content in general) [20]. Besides, a recent study also showed that NINJ1 functions as a bona fide determinant of plasma membrane biomechanical properties [29]. This membrane-rupturing protein was found to regulate plasma membrane fragility also under mechanical strain [29]. The authors reported that NINJ1 weakens the plasma membrane in lytic cell death [29]. Furthermore, the inhibition of plasma membrane rupture using NINJ1 antibodies or by the inhibition of NINJ1 oligomerization (such as by glycine or muscimol) were shown to limit tissue injury in different animal models, such as liver ischemia–reperfusion injury model [30; 31; 32]. However, to our knowledge, the regulation of NINJ1 expression and NINJ1-mediated plasma membrane rupture during lytic cell death has not been previously studied in the context of myocardial ischemia/reperfusion injury.

2. Results and discussion

Here, by analyzing publicly available transcriptomics datasets in silico [33; 34], we found that, myocardial ischemia/reperfusion significantly increases NINJ1 expression in the heart tissue of mice and rats, at the mRNA level (Figure 1, p = 2.4e-07 and 0.0013, respectively). More specifically, myocardial I/R resulted in more than 40% increase in NINJ1 transcript levels in cardiac tissue compared to that of control mice (relative expression of 117.28 vs 82.72, respectively, for control and myocardial ischemia reperfusion) (Figure 1A). In rat heart tissue, myocardial I/R even increased NINJ1 mRNA expression around 70% (3048.8 vs 5152.22, respectively, for control and myocardial ischemia reperfusion) (Figure 1B). This shows that myocardial ischemia/reperfusion markedly upregulates NINJ1 mRNA expression in heart tissue of both mice and rats (Figure 1). In support, we found that the mRNA expression of HMGB1, a large pro-inflammatory protein which can only be released from dying cells following NINJ1-mediated PMR, is increased following myocardial ischemia/reperfusion in rat cardiac tissue (Figure 2, p = 0.041), suggesting that ischemic myocardium response to reperfusion also involves the upregulation of HMGB1 in addition to that of NINJ1 in rats, pointing to the coordinated regulation of lytic cell death and inflammation in myocardial I/R.

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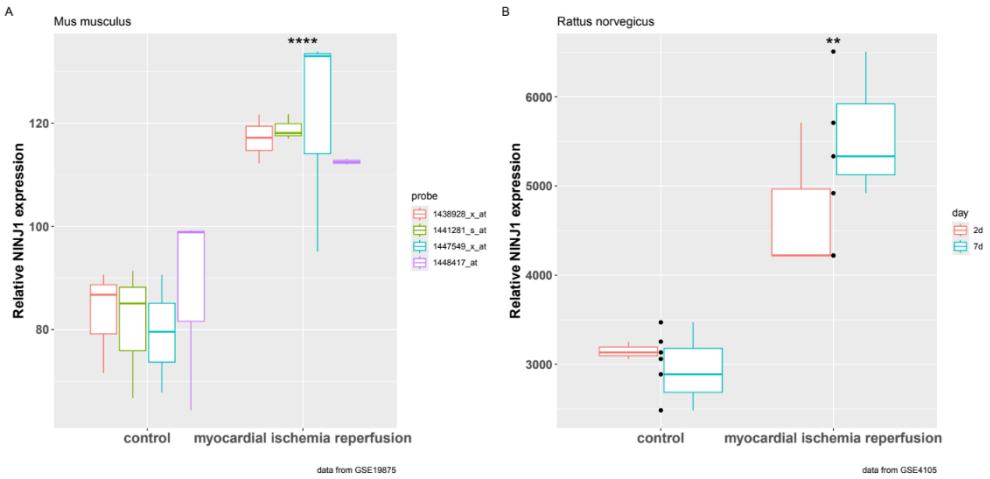

Fig 1. Relative mRNA expression of NINJ1 in the heart tissue of mice (Mus musculus) (A) and rats (Rattus norvegicus) (B) following myocardial ischemia/reperfusion (I/R).[1]

Although the involvement of different regulated cell death modalities in myocardial ischemia/reperfusion injury have been extensively studied in recent years [2; 3; 6; 7; 1; 8; 9; 10; 11; 12; 13; 14; 15], subsequent plasma membrane rupture and lytic cardiomyocyte cell death remains understudied in this context. Here, we showed that myocardial ischemia/reperfusion results in the upregulation of NINJ1 mRNA expression in heart tissue of mice and rats, by performing in silico analysis of previously published gene expression datasets. This is the first study reporting the upregulation of NINJ1 expression at the transcriptional level following myocardial I/R in cardiac tissue. Since NINJ1 mediates plasma membrane rupture and lytic cell death following most cell death mechanisms [18; 23], its increased expression at the transcriptional level in response to myocardial ischemia/reperfusion might hypothetically sensitize cardiomyocytes to increased plasma membrane permeability/rupture and ultimate lytic cell death; however, further experimental data is needed to test this hypothesis. Since plasma membrane pores (such as gasdermin pores in pyroptosis) formed prior to plasma membrane rupture are reversible and releases only smaller pro-inflammatory molecules (such as IL-18), their influence on inflammation might be limited [18; 35]. However, since NINJ1-mediated plasma membrane rupture is irreversible and leads to the release of larger pro-inflammatory molecules (including HMGB1) and lytic cell death, it might lead to an increased inflammatory response and higher number of cell death, possibly resulting in more severe cardiac injury. Furthermore, NINJ1 might hypothetically be a more critical therapeutic target in the treatment of myocardial I/R injury, since it represents a common membrane-rupturing protein during most cell death programs, compared to specific proteins functioning in specific cell death mechanisms. However, a very recent study identified another membrane-rupturing protein (similar to NINJ1) in necroptosis (SIGLEC12 protein) [22; 36]; thus, in theory, combined inhibition of both proteins with membrane-rupturing potential (i.e. both NINJ1 and SIGLEC12) might be a potentially more effective treatment strategy in myocardial I/R injury, since there is extensive crosstalk, interplay and intricate interactions among these different cell death mechanisms in myocardial I/R injury [3]. Further mechanistic studies and experimental validation are needed to better understand the involvement of NINJ1 in lytic cardiomyocyte cell death following I/R and in myocardial I/R injury in order to be able to possibly develop NINJ1-targeting strategies in this condition. These hypotheses based on NINJ1 upregulation at the mRNA level following I/R injury in the heart tissue should also be tested at the protein and functional levels (e.g. by performing NJNJ1 oligomerization experiments) to support the proposed role of NINJ1 in myocardial I/R injury.

[1] Gene expressin data was obtained from GEO using the given GEO accession IDs [43]. In A, different colors represent different probes used for NINJ1 mRNA expression profiling. In B, different colors represent the days when heart ventricles were collected after reperfusion. More experimental detail on the datasets can be found in GEO and refs [33, 34]. **: p <= 0.01; ****: p <= 0.0001. For GSE19875, sample size n(control) = 6, n(myocardial ischemia reperfusion) = 6 for each probe [33]. For GSE4105, n(control) = 6, n(myocardial ischemia reperfusion) = 6 [34]. When the normal distribution of the data could be assumed, t-test was performed to compare group means; otherwise, group means were statistically compared by wilcox test. Data analysis and visualization was completely performed in R programming environment as previously reported [44].

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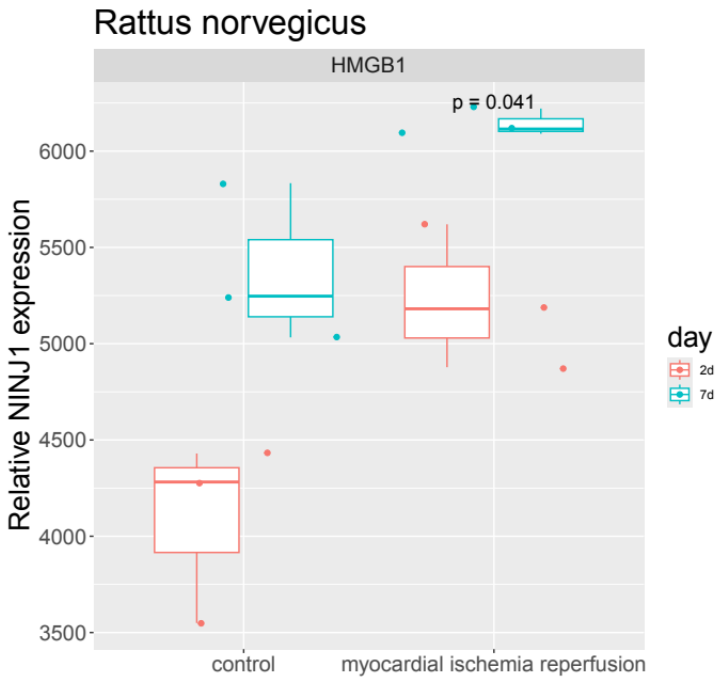

Fig 2. Relative mRNA expression of HMGB1, a large pro-inflammatory protein which can only be released to the extracellular space after NINJ1-mediated PMR, in the heart tissue of rats (Rattus norvegicus) following myocardial ischemia/reperfusion (I/R).[2]

Limitations of the study

Major limitations of the current study include the use of only transcriptomic data (re-analysis of two previously published and publicly available GEO transcriptomics datasets, and the absence of protein validation / lack of proteomics data showing NINJ1 protein level changes following I/R in heart tissue), the absence of functional/mechanistic experiments and of experimental validation (qPCR, Western blot, immunohistochemistry, NINJ1 oligomerization/localization experiments etc.), lack of human data/datasets, and also the reliance on previously published datasets with moderate sample sizes. These significantly limit the strength of the conclusions in the current study. For instance, whether increased NINJ1 mRNA levels lead to increased NINJ1 oligomerization in the plasma membrane, increased number of plasma membrane rupture events, increased DAMP release, and worse cardiac injury should be experimentally tested in the future research.

It should also be clearly stated here that this study propose a hypothesis for future work rather than presenting a proven mechanistic link between increased NINJ1 mRNA levels following I/R and higher number of lytic cell death events in the heart tissue.

3. Materials and methods

Datasets

In the present study, following transcriptomics datasets (which are publicly available at GEO) were analyzed programmatically: GSE19875 (expression data from Mus musculus) [33] and GSE4105 (expression data from Rattus norvegicus) [34]. For GSE19875, sample size n(control) = 6, n(myocardial ischemia reperfusion) = 6 for each probe (total number of probes is four) [33]. For GSE4105, n(control) = 6, n(myocardial ischemia reperfusion) = 6. Gene expression values obtained from GEO were imported into R using read_excel() function from readxl package [37, 38]. The terms “NINJ1” and “ischemia reperfusion” were queried in GEO, no resultant dataset was excluded from the further analysis. For GSE19875 dataset, mean gene expression values for control samples were normalized to 100 for each probe independently (corresponding gene

[2] Different colors represent the days when heart ventricles were collected after reperfusion (2d: heart ventricles were collected two days after reperfusion; 7d: heart ventricles were collected seven days after reperfusion).

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expression values for “myocardial ischemia reperfusion” case were calculated accordingly), and then normalized data from four different probes were combined and analyzed.

Data analysis and visualization

All data analysis and visualization steps in the current study were performed in R statistical programming environment (R version 4.2.1) with RStudio IDE [39] using following R packages: readxl (version ‘1.4.3’) [38], tidyverse (version ‘2.0.0’) [40], and ggpubr (version ‘0.6.0’) [41]. The normality of the gene expression data was tested using Shapiro-Wilk normality test in each dataset [42], using shapiro.test() function from ggpubr package. If the calculated p value < 0.05, we could assume normal distribution of the data, and therefore, performed t-test; otherwise, we compared group means by wilcox test. The following convention for symbols indicating statistical significance was used in the plots: ns (non-significant): p > 0.05; *: p <= 0.05; **: p <= 0.01; ***: p <= 0.001, and ****: p <= 0.0001. Dataset information (GEO accession IDs, etc.) was also given in figure captions [43].

4. Conclusion

NINJ1-mediated plasma membrane rupture and lytic cell death might be involved in myocardial ischemia/reperfusion (I/R) injury in mouse and rat models; however, further mechanistic research is needed.

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