MEDICAL SCIENCE MONITOR

LAB/IN VITRO RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2017; 23: 5876-5884
DOI: 10.12659/MSM.907542

Received: 2017.10.13
Accepted: 2017.11.21
Published: 2017.12.11

MicroRNA-146b-5p Identified in Porcine Liver Donation Model is Associated with Early Allograft Dysfunction in Human Liver Transplantation

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Statistical Analysis C
Data Interpretation D
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Source of support: This study was supported by the National Natural Science Foundation of China (81373156 and 81471583), the Special Fund for Science Research by the Ministry of Health (201302009), the Key Clinical Specialty Construction Project of the National Health and Family Planning Commission of the People's Republic of China, the Guangdong Provincial Key Laboratory Construction Projection on Organ Donation and Transplant Immunology (2013A061401007), Guangdong Provincial International Cooperation Base of Science and Technology (Organ Transplantation) (2015B050501002), Guangdong Provincial Natural Science Funds for Major Basic Science Culture Project (2015A030308010), Guangdong Provincial Natural Science Funds for Distinguished Young Scholars (2015A030306025), Special Support Program for Training High-level Talents in Guangdong Province (2015TQ01R168), and the Pearl River Nova Program of Guangzhou (201506010014)

Background: Poor transplant outcome was observed in donation after brain death followed by circulatory death (DBCD), since the donor organs suffered both cytokine storm of brain death and warm ischemia injury. MicroRNAs (miRNAs) have emerged as promising disease biomarkers, so we sought to establish a miRNA signature of porcine DBCD and verify the findings in human liver transplantation.

Material/Methods: MiRNA expression was determined with miRNA sequencing in 3 types of the porcine model of organ donation, including donation after brain death (DBD) group, donation after circulatory death (DCD) group, and DBCD group. Bioinformatics analysis was performed to reveal the potential regulatory behavior of target miRNA. Human liver graft biopsy samples after reperfusion detected by fluorescence *in situ* hybridization were used to verify the expression of target miRNA.

Results: We compared miRNA expression profiles of the 3 donation types. The porcine liver graft miR-146b was significantly increased and selected in the DBCD group versus in the DBD and DCD groups. The donor liver expression of human miR-146b-5p, which is homologous to porcine miR-146b, was further examined in 42 cases of human liver transplantations. High expression of miR-146b-5p successfully predicted the post-transplant early allograft dysfunction (EAD) with the area under the ROC curve (AUC) 0.759 (P=0.004).

Conclusions: Our results revealed the miRNA signature of DBCD liver grafts for the first time. The miR-146b-5p may have important clinical implications for monitoring liver graft function and predicating transplant outcomes.

MeSH Keywords: Biological Markers • Liver Transplantation • MicroRNAs • Tissue and Organ Procurement

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/907542

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Background

Due to the great efforts of the China Transplantation Society, organ donation in China has developed dramatically since 2011. Since January 2015, donation after donor death has been the only source of deceased organ transplantation in China [1]. Due to cultural differences and absence of laws regarding brain death, 3 types of deceased organ donation were defined: Category I, which is organ donation after brain death (DBD); Category II, which is organ donation after circulatory death (DCD); and Category III, which is organ donation after brain death followed by circulatory death (DBCD) [2]. DBCD provides an option for traditional families who do not fully accept the brain death criteria in China. To date, DBCD has accounted for the largest proportion of donors in China. It is widely accepted that DCD organs have inferior transplantation outcomes due to prolonged warm ischemia time [3]. For DBCD, organ donor should first have a brain death cytokine storm when brain death occurs, and subsequently sustain a warm ischemia injury. However, few studies have focused on recipient outcome using DBCD organs because it is a unique process in the Chinese organ donation system. DBCD is rarely used in Western countries and only in donors who sustain uncontrolled cardiac arrest after brain death diagnosis (classified as Maastricht type IV donation) [4]. A recent cohort study reported that a relatively high proportion (25.8%) of patients developed delayed graft function (DGF) after DBCD kidney transplantation [5]. The increasing proportion of liver transplants now derived from DBCD donors may result in higher risk of complications such as EAD, primary non-function (PNF), and ischemia type biliary lesions (ITBL).

MicroRNAs (miRNAs) are small noncoding RNAs reported to be associated with various physiological or pathological processes [6–8]. Of note, miRNA expression may be an excellent biomarker of donation organ function and injury [9]. Furthermore, with the use of high-throughput sequencing technologies, bioinformatics, and biostatistics, the increasing understanding of the molecular mechanism of donor organ injury may provide a novel method for treatment in clinical transplantation [10]. We previously established a DBCD porcine model to investigate liver graft pathologic injury and compared it with DBD and DCD grafts [11]. In the present study, we analyzed the miRNA profile in liver grafts between 3 organ donation categories in China and screened the specific miRNAs that may regulate liver injury in DBCD. We also evaluated the prognostic value of miRNA of liver grafts in EAD after LT.

Material and Methods

Animals

Twelve pigs (4–6 months old, 22.5±3.9 kg) were obtained from the Experimental Animal Center of South Medical University, China. Pigs were sedated with ketamine (10 mg/kg) in combination with fentanyl (4 μg/kg). Anesthesia was induced by 5% isoflurane and atracurium (0.5 mg/kg). During surgery, the concentration of isoflurane was maintained at 2% and pigs were artificially ventilated. The experimental protocol was approved by the Committee for Animal Experiments of Sun Yat-sen University.

Organ procurement protocol

Organ procurement in this experiment was conducted according to the protocols for China Category I (DBD group), II (DCD group), and III (DBCD group) [12]. In the DBD group (n=3), brain death was induced by continuous high intracranial pressure using an expanding balloon. After diagnosing brain death twice within 12 h, organ procurement was performed. In the **DBCD group** (n=3), brain death was induced as previously described. After confirming brain death twice, cardiac death was induced by withdrawal of ventilation. Liver procurement was performed after 5 min of no-touch time. In the **DCD group** (n=3), cardiac death was induced by intravenous injection of potassium chloride. Organ harvesting was performed at 1 h after cardiac death diagnosis. The donor livers were perfused *in situ* with 1 L hypertonic citrate adenine solution and 1 L Celsior solution at 4°C. Donor livers were stored in Celsior solution for 4 h. All tissue samples were collected from the same region of the livers.

miRNA sequencing

Total RNA from 3 porcine liver samples was extracted using TRIzol reagent (Thermo Fisher Scientific, Waltham, MA, USA) and an miRNeasy kit (Qiagen, Germantown, MD, USA). Total RNA from each sample was used to prepare the miRNA sequencing library. Then, the sequencing was performed on an Illumina HiSeq 2000 device (Illumina, San Diego, CA, USA). The threshold value we used to screen differentially expressed miRNAs was fold change ≥2.0 or fold change ≤0.5 and P value <0.05.

GO and pathway analysis

Fisher's exact test in Bioconductor's topGO was used to assess if there is more overlap between the DE list and the GO annotation list than would be expected by chance. The P value produced by topGO denotes the significance of GO terms enrichment in the DE genes. Pathway analysis is a functional analysis for mapping genes to KEGG pathways. The P value denotes the significance of the pathway correlated to the conditions.

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Fluorescence *in situ* hybridization

According to miRBase (*http://www.mirbase.org*), hsa-miR-146b-5p is highly homologous to ssc-miR-146b. Details of miR-146b sequence in pigs and humans are shown in Supplementary Table 1. FISH-based miR-146b-5p imaging was performed based on a previously described protocol [13]. Briefly, after deparaffinized, the endogenous peroxidase was quenched with 0.024 M HCl in ethanol, incubated with proteinase K (20 µg/ml, 37°C for 10 min), and hybridized overnight at 37°C with probe specific to miR-146b at the concentration of 8 ng/uL. Locked nucleic acid-based miR-146b probe was labeled with CY3 at the 5' end. The probe sequence was 5'-AGCCTATGGAATTCAGTTCTCA-3'. Finally, the anti-biotin-labeled fluorescein isothiocyanate was used to visualize the positive hybridization signals, and the images were observed using fluorescent microscopy (Nikon, Eclipse CI, Tokyo, Japan).

Donors and recipients

The organ donation process was conducted as previously described. A liver graft sample was obtained 90 min post-reperfusion from each recipient. Recipients' early allograft dysfunction (EAD) was defined if 1 or more criteria were met: Bilirubin ≥171 µmol/L on post-operation day (POD) 7; international normalized ratio (INR) ≥1.6 on POD 7; and aminotransferase level (AST or ALT) >2000 U/L within POD 7 [14,15]. Our donation program is in line with the policy of the voluntary organ donation system and is consistent with the World Health Organization's guiding principles and with the Declaration of Istanbul on organ transplantation. The protocol for this study was approved by the Ethics Committee at the First Affiliated Hospital of Sun Yat-sen University.

Statistical analysis

Continuous variables were compared using the *t* test or one-way ANOVA. An ROC curve was obtained to evaluate the predictive value related to EAD post-transplantation. *P* value <0.05 was considered as a significant difference. All statistical analyses were conducted using Statistical Product and Service Solutions 20.0 (SPSS Inc., Chicago, IL).

Results

miRNA profile in DBCD group *vs.* DBD and DCD groups

The general animal model design is shown in Figure 1. To investigate the potential role of miRNA in liver graft donation, we first set up the 3 different organ procurement protocols in porcine models (n=3 in each group), which is in accordance with clinical practice in the China organ donation system. Liver

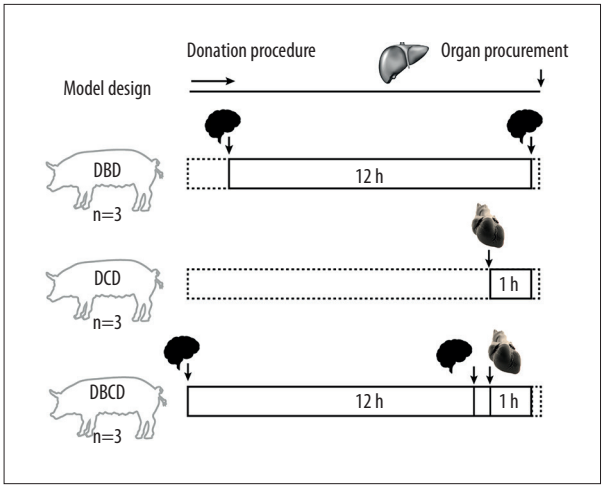

Figure 1. The study design of the experiment porcine model of DBD, DCD, and DBCD.

graft samples were harvested as previously mentioned for next-generation sequencing. Expression profiles in the DBCD, DBD, and DCD groups were assessed with miRNA-sequence analysis. The strongly differentially expressed miRNAs (fold change ≥2 or ≤0.5, $P<0.05$) in liver grafts between DBCD *vs.* DBD and DBCD *vs.* DCD were hierarchically clustered and are shown in a heat map (Figure 2A, 2B). In the DBCD *vs.* DBD group, 40 miRNAs were significantly up-regulated and 19 were significantly down-regulated, as shown in a volcano plot (Figure 3A). In the DBCD *vs.* DCD group, 8 miRNAs were significantly up-regulated and 12 were significantly down-regulated (Figure 3B). Importantly, among those differentially expressed miRNAs, miR-7-2, miR-7-1, and miR-146b were observed to be significantly up-regulated in the DBCD group vs. other groups, while miR-874 was observed to be significantly down-regulated in the DBCD group (Figure 4). These 4 miRNAs, specifically differentially expressed in the DBCD group, were selected for further analyses.

GO analysis and pathway analysis

To further evaluate and predict the functions of miRNAs in DBCD, we used a bioinformatics analysis to reveal the potential behavior of miRNAs. The functional classification method based on gene ontology was used to further evaluate the key function of miRNAs. The GO biological process terms associated with miR-146b are shown in Figure 5A, and suggest that miR-146b plays an important role in I-kappaB kinase/NF-kappaB signaling. KEGG pathway analysis was used to determine the function of miR-146b. The pathways associated with miR-146b targets are shown in Figure 5B. Among these, the NF-kappaB signaling pathway is the most significant. Bioinformatics analysis showed a high correlation in regulating the immune response process. Therefore, miRNA-146b was selected for further validation in human samples.

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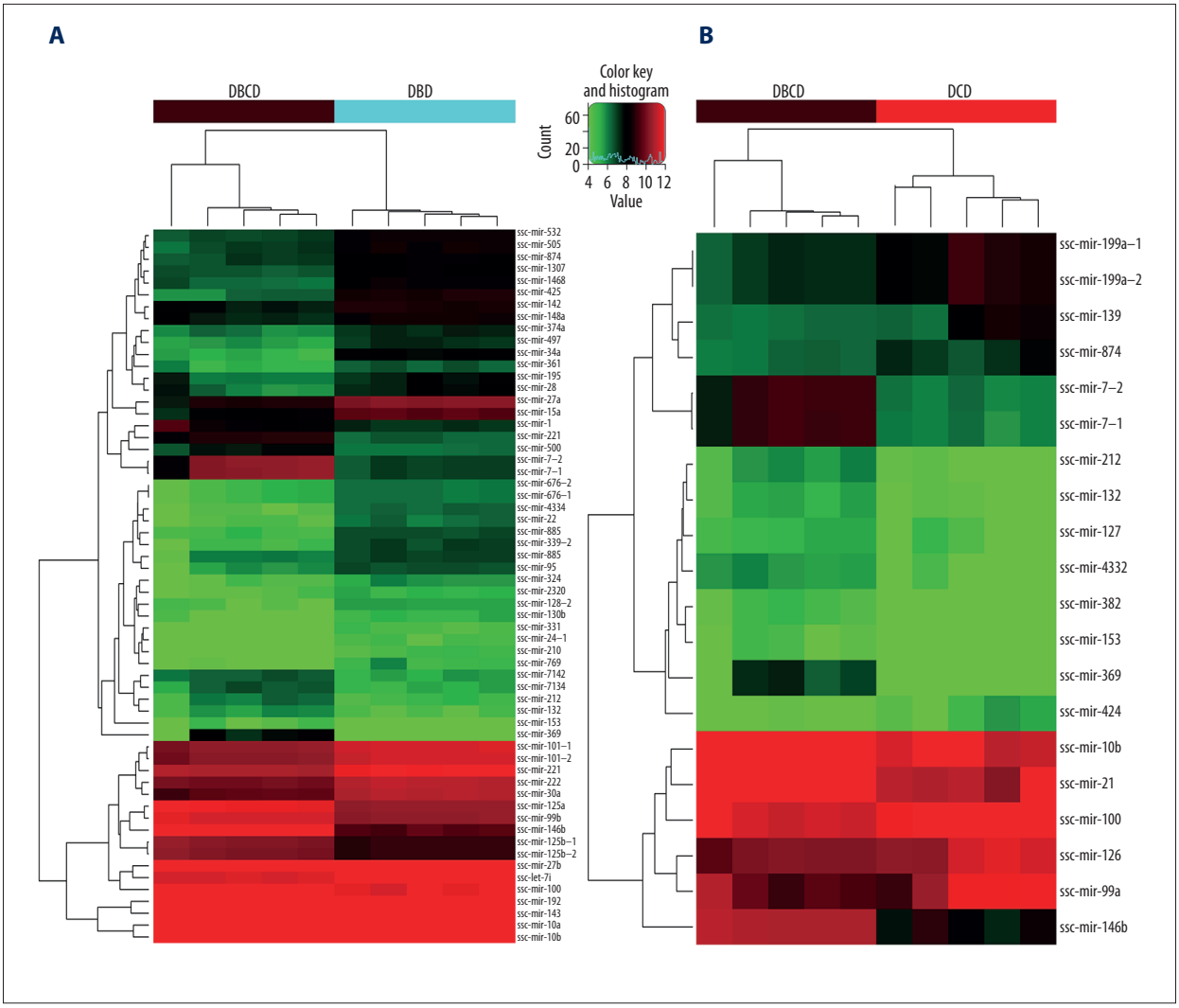

Figure 2. Supervised hierarchical clustering of miRNA expression patterns classified by donation classification. (**A**) Hierarchical clustering of the miRNAs with differential expression between DBCD and DBD. (**B**) Hierarchical clustering of the miRNAs with differential expression between DBCD and DCD. The threshold value of differentially expressed miRNAs is fold change >2.0 or fold change <0.5 and *p* value <0.05.

miR-146b-5p as a biomarker of early allograft dysfunction after liver transplantation

Our previous report shows a relatively high incidence of EAD in recipients using liver grafts from donation in China [16]. The potential of specific miRNA in varying graft quality has not been well investigated, especially in our new China organ donation system. Human miR-146b-5p shares high nucleotide homology with porcine miR-146b. We then sought to determine the relationship between miR-146b-5p in liver grafts and post-LT EAD. We observed 42 liver tissue biopsies at 90 min after reperfusion during LT. Among these, 22 patients developed EAD and 20 patients obtained immediate graft function (IGF). Expression of miRNA-146b-5p in liver graft were detected by FISH. The result indicated that the miRNA-146b-5p level was significantly higher in the recipients with EAD compared to the IGF group (Figure 6A, 6B). To explore the predictive effects on EAD, we further determined the prognostic value of miR-146b-5p by using ROC curve analysis. The area under the curve was 0.759 (95% CI 0.611–0.907, *P*=0.004) (Figure 6C).

Discussion

DBCD, based on the Chinese culture and socioeconomic context[2], is a unique practice in the Chinese donor classification system. The pathophysiology changes, including brain death cytokine storm and subsequent IRI during cardiac death, can impair donor organ functions. As a novel clinical practice, there have been few reports on DBCD liver graft survival and

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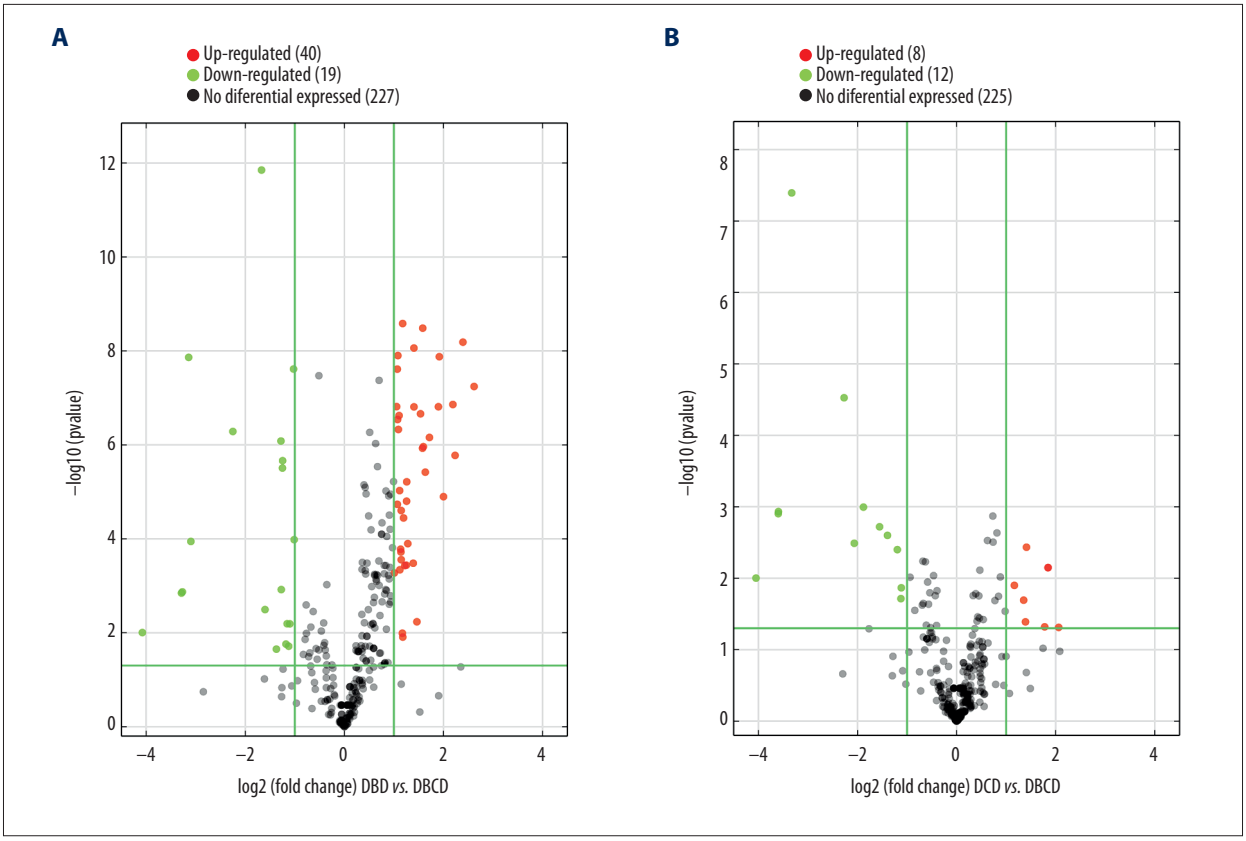

Figure 3. Volcano plot of differentially expressed miRNA in DBD *vs.* DBCD (**A**) and DCD versus DBCD (**B**). Horizontal axis represents fold change (log2 transformed). Vertical axis represents *P* value (-log10 transformed). Up-regulated miRNAs are shown in red and down-regulated miRNAs are shown in green.

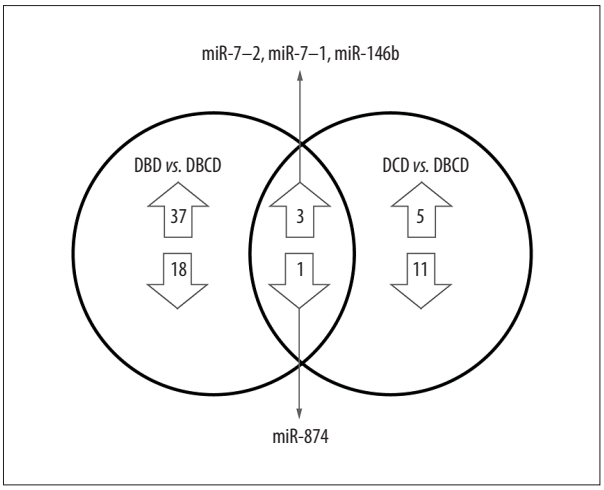

Figure 4. Comparison of miRNA expression in DBD *vs.* DBCD and DCD *vs.* DBCD. The Venn diagram shows the number of differentially expressed miRNAs. The overlapping section represents 4 shared miRNAs among the 2 comparison groups.

donor-related complications. We previously reported that the incidence of EAD after LT is 34.6% in our single center [16]. Thus, the graft quality of organs from DBCD in LT is still controversial, especially in China.

Given their importance in regulating gene expression, miRNAs are a potential biomarker of organ quality in solid organ transplantation, and are associated with this pathophysiological process [9]. In LT, miRNAs have been reported to be sensitive biomarkers in acute rejection and HCV recurrence [17,18]. To assess molecular processes in IRI during LT, Gehrau RC et al. compare the miRNA expression in the liver between biopsies at preimplantation and at 90 min post-reperfusion [19]. In a DCD LT model, the expression of miR-22 was observed to be lower in the PNF group, but showed a low diagnostic potential in recognizing poor liver quality [20]. In the present study, we first developed a porcine organ donation model, and then collected the liver samples for miRNA sequencing.

Among the differentially expressed miRNAs, miR-146b was specifically up-regulated in the DBCD group and was thus selected for further analyses. The important roles of miR-146 have been shown in different biological processes and diseases in

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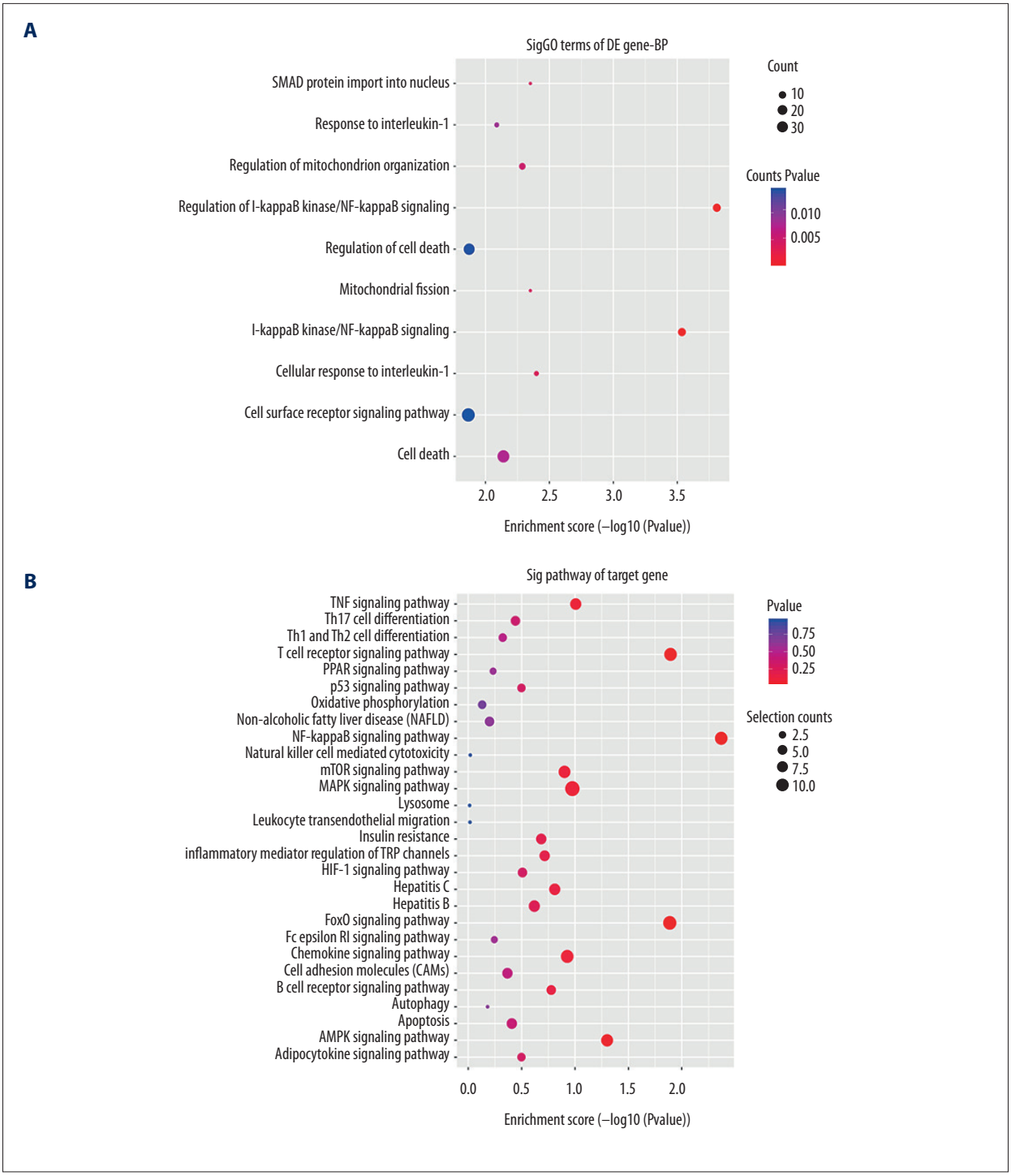

Figure 5. The function prediction of miRNA-146b. GO and pathway analyses were performed based on the miRNA-146b-associated mRNAs. Top GO terms (**A**) and pathways (**B**) are shown in the figure. Dot color represents *P* value (-log10 transformed) and dot size represents quantity.

previous studies, especially in fine-adjusting the immune responses [21,22]. The miR-146 family is mainly constructed by 2 genes, miR-146a and miR-146b, and is highly conserved in most vertebrates. For example, miR-146a acts as a negative regulator of autoimmunity, myeloid cell proliferation, and oncogenic transformation [23]. In a more recent study, miR-146b knockdown enhanced the tumor necrosis factor receptor-associated factor 6 (TRAF6), which in turn activated the NF-κB

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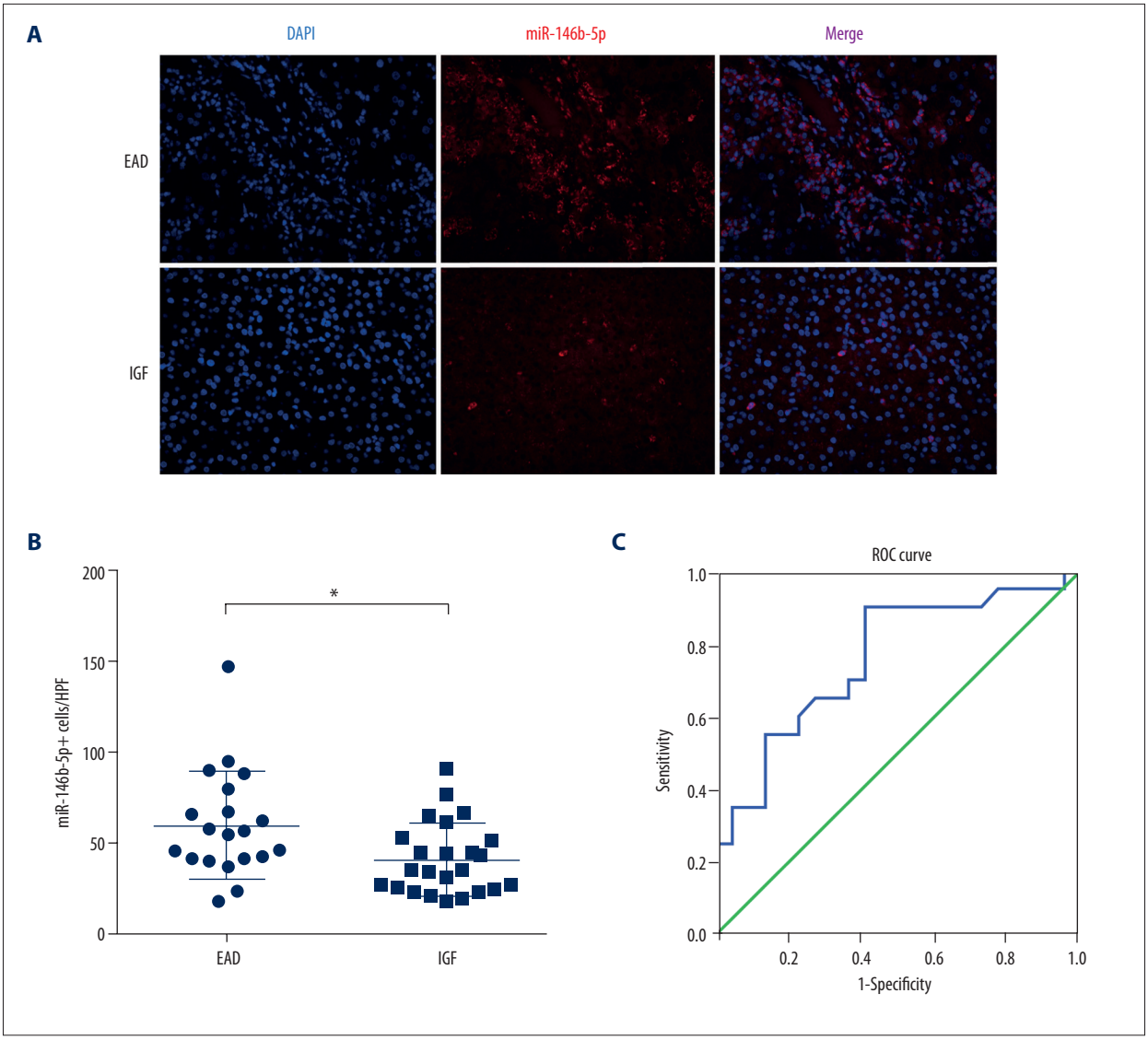

Figure 6. miRNA-146b-5p expression increases in liver graft from recipients who develop EAD. (**A**) Representative FISH image of miRNA-146b-5p expression in EAD and IGF recipients' liver grafts. (**B**) miRNA-146b-5p expression in EAD (n=22) and IGF (n=20) recipients' liver grafts. (**C**) ROC curve for expression of miRNA-146b-5p with respect to recipients' EAD.

pathway, and further enhanced regulatory T cells in graft-versus-host disease [24]. Our GO and pathway analysis confirmed that miR-146b has a role in immune response regulation.

In recent studies, there has been increased interest in miR-146b in IRI. Overexpression of miR-146b is reported to protect against myocardial IRI through targeting Smad4 [25]. However, in a rat IRI model, downregulation of miR-146b ameliorate injury by inhibiting TRAF6 and blocking the NF-κB pathway in the liver [26]. In the present study, the potential mechanism of miR-146b in DBCD liver graft may be related to inflammatory responses triggered by simultaneous brain death and heart death. Therefore, knockdown or overexpression of miRNA requires further investigation to be verified as a therapeutic method to rescue marginal grafts, such as DBCD organs.

After miR-146b was selected as a biomarker in the porcine experimental DBCD model, we detected the miR-146b-5p expression in liver allograft biopsies of 42 recipients, and showed a favorable prognostic value on EAD. Of note, we only considered miR-146b-5p expression in liver grafts as a key factor. However, we know that donor and recipient factors, as well as surgical factors, can also affect EAD after transplantation. More factors should be included in a new prognostic model, and in this way miR-146b-5p may improve the prognostic value of the new model.

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Early detection of miR-146b-5p for recipients at high risk of EAD is critical to provide monitoring and early therapeutic interventions. Considering that evaluation of miR-146b-5p requires a liver biopsy (an invasive procedure), it may heighten the difficulty during implementations in clinical practice. In an initial pilot study, cholangiocyte-derived miR-30e, miR-222, and miR-296 released in donor liver perfusates were reported to be associated with biliary injury [27]. We should further attempt to measure the expression of miR-146b in perfusates, as a noninvasive way to evaluate liver grafts.

Conclusions

These findings identify a specific miR-146b up-regulated in DBCD *vs.* DCD and DBD in a porcine liver donation model. The increase of miR-146b-5p was confirmed in EAD recipient liver grafts biopsies. We found that miR-146b-5p expression in liver grafts is correlated with EAD, which is a potential biomarker to evaluate organ quality. However, the liver biopsies were observed after reperfusion, which limited the application in evaluating graft viability before LT. The underlying mechanism and therapeutic effect of miR-146b in DBCD inflammatory response require further investigation.

Abbreviations

DBD – organ donation after brain death; DCD – organ donation after cardiac death; DBCD – organ donation after brain death followed by cardiac death; LT – liver transplantation; EAD – early allograft dysfunction; PNF – primary non-function; ITBL – ischemia type biliary lesions; miRNA – microRNA; GO – Gene Ontology; FISH – fluorescence *in situ* hybridization; IGF – immediate graft function; POD – post-operation day; INR – international normalized ratio; AST – aspartate transaminase; ALT – alanine transaminase; ROC curve – receiver operator characteristic curve; TRAF6 – tumor necrosis factor receptor-associated factor 6; IRI – ischemia reperfusion injury-induced; HCV – hepatitis C virus

Supplementary Table

Supplementary Table 1. miRNA sequences of miR-146b.

miRNA ID	Sequence
ssc-miR-146b	ugagaacugaauuccauaggc
hsa-miR-146b-5p	ugagaacugaauuccauaggcu

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