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SEQUENCE CHARACTERISTICS AND EXPRESSION LOCALIZATION ANALYSIS OF INTERCELLULAR ADHESION MOLECULES 2

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ABSTRACT

ICAM2 is a member of the immunoglobulin superfamily and plays an important role in inflammatory response and xenograft rejection. This study aimed to analyze the expression regulation pattern, sequence characteristics and potential biological functions of *ICAM2* gene in the Banna mini-pig inbred lines. The results showed that the full-length CDS of *ICAM2* gene was 834 bp, encoding 277 amino acids, including 11 exons and 10 introns. The *ICAM2* gene contained two conserved domains, which were members of the ICAM_N family and the Ig superfamily; the gene has a transmembrane helix and a signal peptide sequence. Multi-species phylogenetic tree analysis revealed that the gene was highly conserved in Rodentia, Primates, Perissodactyla and Artiodactyla. Protein-protein interaction network analysis indicated that ICAM2 interacted closely with ICAM1, ITGAL, ICAM3, ITGB2 and MSN. *ICAM2* mRNA was highly expressed in tissues such as the liver, spleen, lymph nodes and tonsils, and its protein was mainly expressed in the cytoplasm. In summary, these findings laid the foundation for future studies on the role of the *ICMA2* gene in key biological processes such as the immune system of BMI pigs and xenotransplantation immune rejection.

Key words: Immune rejection, *ICAM2*, Expression, Subcellular localization.

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INTRODUCTION

The shortage of human organs has led to intense interest in using pig organs for clinical transplantation, and in-depth studies of the mechanisms by which human immune cells interact with porcine endothelial cells are particularly important. Cellular adhesion plays a crucial role in normal hemostasis and inflammation, necessitating interactions among platelets, endothelial cells, and leukocytes. These adhesion events are orchestrated by specific molecular interactions involving members from at least five classes of molecules: integrins, members of the immunoglobulin superfamily (IgSF), C-type lectins, carbohydrates, and extracellular matrix proteins, the latter acting as lectin counter structures (Celi *et al*. 1997). The preservation of functional characteristics across species boundaries suggests that porcine Intercellular Adhesion Molecule 2 (*ICAM2*) may play a role in cellular interactions linked to xenograft rejection (Godwin *et al*. 2004). *ICAM1*, *ICAM2*, and *ICAM3* belong to the immunoglobulin superfamily of adhesion molecules. The interaction between ICAM/LFA-1 (lymphocyte function-associated antigen-1) is crucial in various immune and inflammatory processes. This interaction plays a significant role in immune surveillance, T cell-mediated killing, T helper/B cell responses, and the extravasation of leukocytes (Springer 1994; Salomon and Bluestone 1998). ICAM, a constituent of the immunoglobulin supergene family of adhesion proteins, particularly highlights *ICAM1* as a costimulatory molecule essential for immune activation (Chong *et al*. 1994). *ICAM1* and *ICAM2* exhibit roles in immune trafficking that share similarities but also possess distinct functions, suggesting a degree of overlap and synergy in their contributions to immune processes (Bleijs *et al*. 1999).

ICAM2 is present on the surface of endothelial cells, neutrophils, platelets, and various other leukocyte subsets. Its expression contributes to neutrophil-mediated vascular permeability and the subsequent leakage of plasma (Lyck and Enzmann 2015). Research involving *ICAM2*-deficient mice has provided insights into the role of *ICAM2* in critical biological processes like lymphocyte recirculation, trafficking, and extravasation. These studies indicate that inflammatory responses show enhanced eosinophil trafficking in the absence of *ICAM2* (Gerwin *et al*. 1999). *ICAM2* has a distinct role from *ICAM1* in T cell-mediated co-stimulation (Heiska *et al*. 1998). *ICAM2*

plays an important role in dendritic cell trafficking through its ligand and plays a role in cell perturbation associated with xenotransplantation (Geijtenbeek *et al*. 2000; Godwin *et al*. 2004). In this study, firstly, cloning the *ICAM2* gene, its sequence characteristics and functions were analyzed. Then, the expression of this gene in multiple tissues was detected and its location in cells was determined. The purpose of this study is to lay a foundation for the study of the molecular mechanism of immune rejection during porcine-human xenotransplantation.

MATERIALS AND METHODS

The experiments involving animals were conducted in accordance with the 2006 national guidelines for experimental animal welfare announced by the Ministry of Science and Technology of the People's Republic of China (Guiding Opinions on Kindly Treating Laboratory Animals). Furthermore, it has obtained approval from the Animal Welfare and Research Ethics Committee of the Research Ethics Committee at Yunnan Agricultural University, Kunming, China (Approval No. YNAUREC2020224).

Experimental Animals and Study Protocols: Three individuals from Banna mini-pig inbred lines, each at the age of 12 months, were sourced from stock farms located in Kunming, China. A total of fifteen tissue samples, comprising the heart, liver, spleen, lung, kidney, skin, ileum, appendix, brain, spinal cord, lymph nodes, tonsils, adrenal, thyroid, and submandibular glands, were collected and stored at -80℃ in a refrigerator for experimental use. The reagents required for the experiment were purchased from TaKaRa Company, Dalian, China.

Amplification and Sequencing of the Gene *ICAM2*: The *ICAM2* gene primers (F/R) was designed based on GenBank pig *ICMA2* mRNA sequence (accession number: NM_001001631). Primers (F: CTCCATCACAGCCGCACTCCT; R: AGCGTTTGCTGCTGCTTGGTA) were designed for the *ICAM2* gene and the full-length coding sequence of the gene was amplified using liver cDNA as a template. The amplified products were sent to China Kunming Tsingke Biotechnology Co., Ltd for sequencing. The *ICAM2* genomic DNA was searched through the Ensembl database (https://www.ensembl.org/index.html) to study the length of the gene, its location on the chromosome, and the number of exons and introns. Adobe Illustrator 2022 software was used to draw schematic diagrams of *ICAM2* genome, mRNA and protein structures.

Molecular function analysis of *ICAM2*: Lasergene 7.1 was utilized to perform nucleic acid sequence alignment and calibration for *ICAM2*. The structure of ICAM2 protein sequence was predicted and analyzed by ProtParam program, SOPMA (secondary structure), ProtScale (hydrophobic structure), TMHMM (transmembrane helix), SignalP (signal peptide). The MEGA-X software was employed to construct the phylogenetic tree of ICAM2 protein. We conducted the protein-protein interaction analysis using String11.5.

Tissue expression profiling by qPCR: The qPCR was conducted to determine the *ICAM2* mRNA expression in 15 porcine tissues and the housekeeping gene *GAPDH* as the endogenous control. The primers used for testing the control gene were 5′-CCTTCATTGACCTCCACTACATGGT -3′(forward) and 5′- CCACAACATACGTAGCACCAGCATC-3′(reverse). The porcine *ICAM2* primer sets were 5′-ACCACAGCCCTCAGGAAAGAT-3′ (forward and 5′-GACAGATGCCACAAACAAGAAGA-3′(reverse). The 20 μL reaction included 10 μL of Power SYBR Green PCR Master Mix, 8 μL of sterile water, 1 μL of cDNA, 0.5 μL of 10 μM forward primer, and 0.5 μL of 10 μM reverse primer. Amplification was performed with the default settings. The relative expression of PCR products was determined using the $2^{-\Delta\Delta Ct}$ method. The relative expression of PCR products was determined using the $2^{-\Delta\Delta Ct}$ method. This method is one of the more commonly used and convenient methods in real-time fluorescence quantitative PCR data analysis. It is mainly used to determine the impact of experimental treatment on the expression of internal reference genes, and then analyze the relative changes in gene expression in real-time fluorescence quantitative PCR experiments. (Livak and Schmittgen 2001).

Construction of expression vector and subcellular localization detection: Primers for the eukaryotic expression of the *ICAM2* gene were designed by considering the restriction sites within the *ICAM2* gene and the polylinker sites of the eukaryotic expression vector pEGFP-C1, which is used for expressing green fluorescent protein. The upstream and downstream primers were as follows: forward primer (5'-GAATTCATGTCCCCTTTTGATTCCTG-3'), reverse primer (5'-GGATCCTCATGCAAGCTGTGCCTGGT-3'). These primers were designed with the *EcoR* I and *BamH* I restriction sites, respectively. A recombinant eukaryotic expression vector named pEGFP-C1-*ICAM2* was constructed, and this vector was used for transfection in PK15 cells that were previously cultured. Mito Tracker was used to stain the mitochondria of ST cells, and Hoechst33342 was used to stain the nucleus of PK15 cells to determine the localization of target gene expression proteins in the cells.

RESULTS

***ICAM2* gene and genomic information:** The PCR product of *ICAM2* gene is 1012 bp (Figure 1A). The *ICAM2* gene is located between 453003-480820 bp on the pig chromosome (LUXU01076606.1), with a total length of 27817 bp, including 11 exons and 10 introns (Figure 1B)

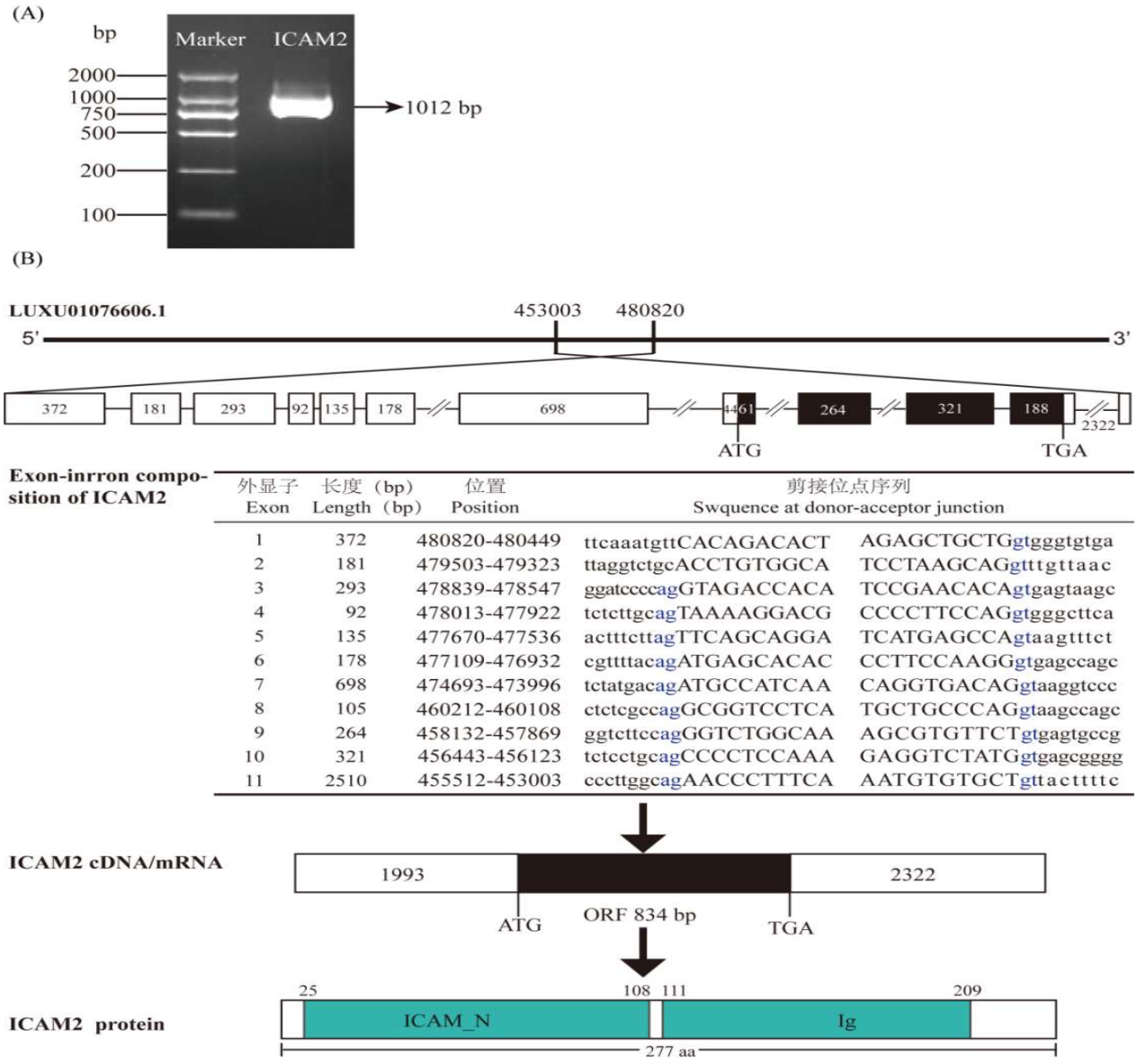

Figure 1. Gene structure of *ICAM2*

(A) RT-PCR product of BMI *ICAM2* gene;M, DL2000 DNA Marker, *ICAM2* is the PCR product of F/R. (B) Genomic structure of ICAM

Domain information for *ICAM2*: The complete CDS of *ICAM2* gene was obtained with a sequence length of 834 bp and encoding 277 amino acids (Figure 2A). The gene has two conserved domains, 25-108 AA belonging to the ICAM_N family and 111-209 AA belonging to the Ig superfamily member (Figure 2B), corresponds to the horizontal line portion of Figure 2A. The gene has one transmembrane helix at position 225-247 AA (Figure 2C), corresponds to the dotted portion of Figure 2A. The amino acid sequence of *ICAM2* N-terminal pre-1-23 AA (MSPFDSWGLFMAFLALLCCPGSG) is the signal peptide sequence, with cleavage sites located between the 23rd AA and 24th AA (Figure 2D), corresponds to the shaded part of Figure 2A.

(A)

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ATGTCCCCTTTTGATTCCTGGGGACTGTTCATGGCCTTTCTCGCCCTGCTCTGCTGCCCAGGGTCTGGCAAGGAGGCGTTCGAGAAACCC  90
 M  S  P  F  D  S  W  G  L  F  M  A  F  L  A  L  L  C  C  P  G  S  G  K  E  A  F  E  K  P  30
ACGTGGACGAAGCAGCTGGTGGTGGAGTCTGGAAGGTCCCAGGTGATTAACTGTAGTGCCAGCTGTACTCAGCCTGAGAACAGTGGTCTG 180
 T  W  T  K  Q  L  V  V  E  S  G  R  S  Q  V  I  N  C  S  A  S  C  T  Q  P  E  N  S  G  L  60
GAGACCACCGTCTCCAAGAAGCTCCTGAAAGAGGGGGCTCAGTGGAAGCTGTATGAGGTCAATGTCTCCCAGGACACCATCCTCCTTTGC 270
 E  T  T  V  S  K  K  L  L  K  E  G  A  Q  W  K  L  Y  E  V  N  V  S  Q  D  T  I  L  L  C  90
TATTTCACCTGCTTCGGCAGGCAGGAGATCAAGAGATTCAACATCAGCGTGTTCTCCCCTCCAAAGCAAGTGCTGCTGACGCTGCAGCCC 360
 Y  F  T  C  F  G  R  Q  E  I  K  R  F  N  I  S  V  F  S  P  P  K  Q  V  L  L  T  L  Q  P  120
ACTTTTGTGACCGTAGGGACATGGTTCACCATCGAGTGCCGGGTGCCCTCTGTGGCCCCCTTTGAAACCCTCACCATCACCCTGCTCCGT 450
 T  F  V  T  V  G  T  W  F  T  I  E  C  R  V  P  S  V  A  P  F  E  T  L  T  I  T  L  L  R  150
GGTAGTGAGATTTTGTACAATGAGACTCTAAGAGGGACCACACCGTCCCCCCAGGAGGCTATAGTGACCCACAACACCACAGCCCTCAGG 540
 G  S  E  I  L  Y  N  E  T  L  R  G  T  T  P  S  P  Q  E  A  I  V  T  H  N  T  T  A  L  R  180
AAAGATGGGCACCACAACTTCACCTGCCAGGCCAAGATGGATCTGCAGTCTCGCGGCGGACACCTCATTCACAGAGTCTCAGATCCCCAG 630
 K  D  G  H  H  N  F  T  C  Q  A  K  M  D  L  Q  S  R  G  G  H  L  I  H  R  V  S  D  P  Q  210
GTGCTTGAGGTCTATGAACCCTTTCAAGACAGCCAGATGGCCATCATCATCGCGGTCGTGTCCGTGCTGCTCTTCTTGTTTGTGGCATCT 720
 V  L  E  V  Y  E  P  F  Q  D  S  Q  M  A  I  I  I  A  V  V  S  V  L  L  F  L  F  V  A  S  240
GTCCTGCTCTGCTTTGTCTTGGGCGAGCACTGGCGCCAGAGGCGGACAGGTTCCTACATGGTGCAAGCCGTTCAGAGGAGGCTGAGGTGG 810
 V  L  L  C  F  V  L  G  E  H  W  R  Q  R  R  T  G  S  Y  M  V  Q  A  V  Q  R  R  L  R  W  270
TGCTACCAGGCACAGCTTGCATGA                                                                    834
 C  Y  Q  A  Q  L  A  *                                                                     277
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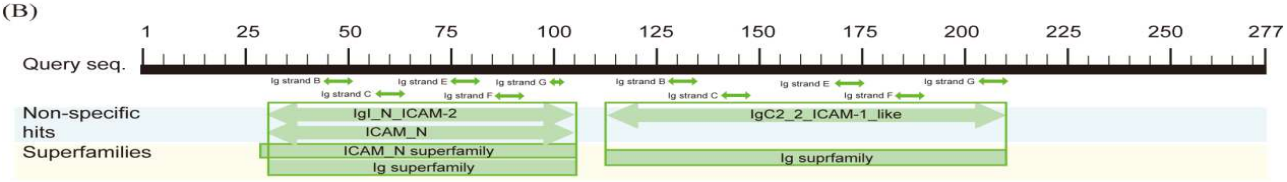
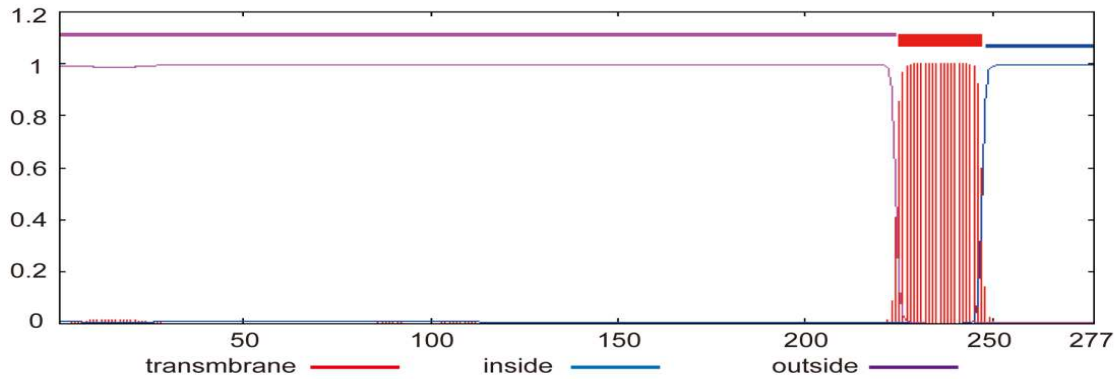
(B)



(C)



(D)

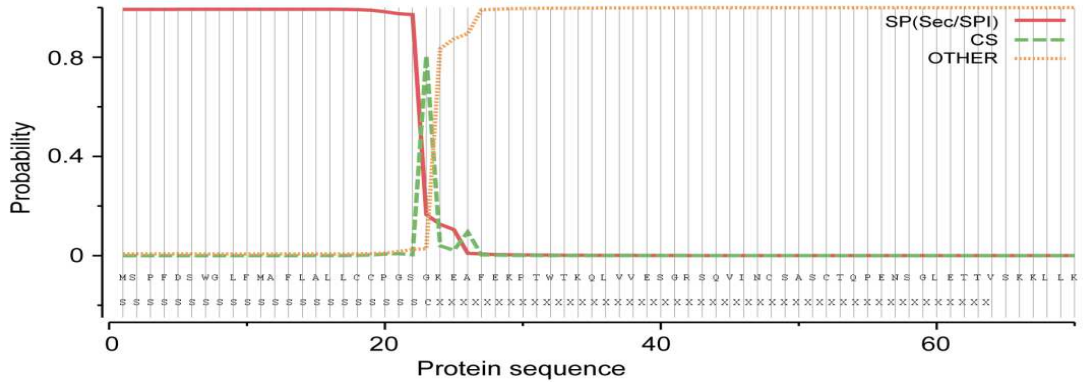


Figure 2. Results of domain analysis of *ICAM2*

(A)The coding sequence of *ICAM2* and its amino acids sequence; (B)conserved domains;(C) transmembrane helical structure; (D)signal peptide sequence

Protein sequence of ICAM2: The molecular weight of porcine ICAM2 protein is 31.31 kD, the isoelectric point is 8.18. the molecular formula is $C_{1411}H_{2211}N_{377}O_{398}S_{15}$, the negative and positive charge residues are 22 and 26, respectively. In the secondary structure of the 277 amino acids of ICAM2, α helix 90 AA (32.49%), extended chain 70 AA (25.27%), β angle 18 AA (6.50%), Random curling 99 AA (35.74%) (Figure 3A). ICAM2 protein has a maximum hydrophobic value of 3.433 at the 229th amino acid and a minimum hydrophobic value of -2.856 at the 252nd amino acid, N-terminal hydrophobic, and C-terminal hydrophilic (Figure 3B).

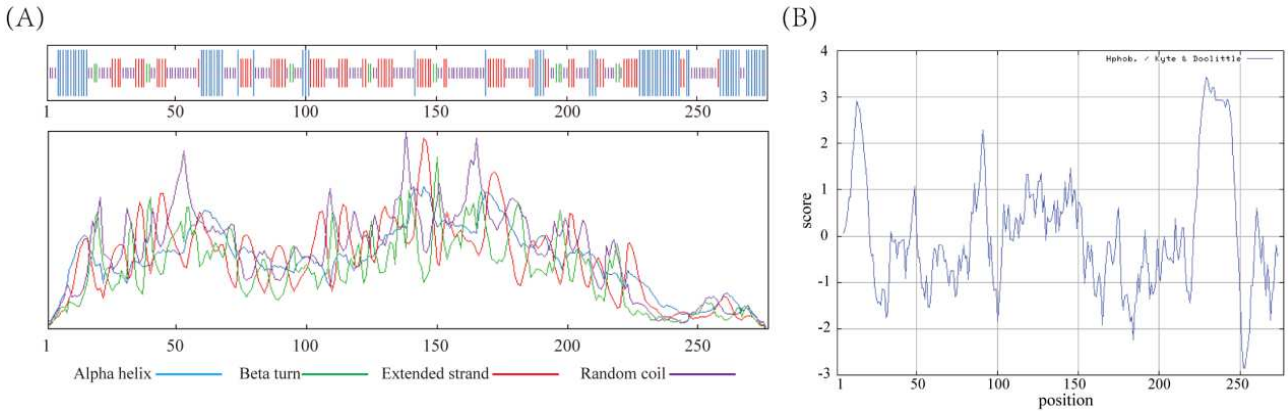


Figure 3. Amino acid sequence analysis results of ICAM2

Construction of a multispecies evolutionary tree: The amino acid sequences of *ICAM2* genes from multiple species were downloaded and compared for sequence similarity analysis. The results showed that the amino acid sequence of BMI *ICAM2* had high similarity with that of mouse (*Mus musculus* CAA46474), rat (*Rattus norvegicus* NP_001007726), chimpanzee (*Pan troglodytes* NP_001009166), human (*Homo sapiens* AF340053_1), horse (*Equus caballus* XP_001495363), donkey (*Equus asinus* XP_014703461), cattle (*Bos taurus* XP_010822547), the similarity scores were all above 51%. Species phylogenetic tree analysis showed that rats and mice were grouped into one group, Rodentia; Chimpanzees and people are grouped together as Primates; Horses and donkeys are grouped together in the order of Perissodactyla; Pigs and cattle are grouped together,all belonging to Artiodactyla, which met the clustering criteria (Figure 4).

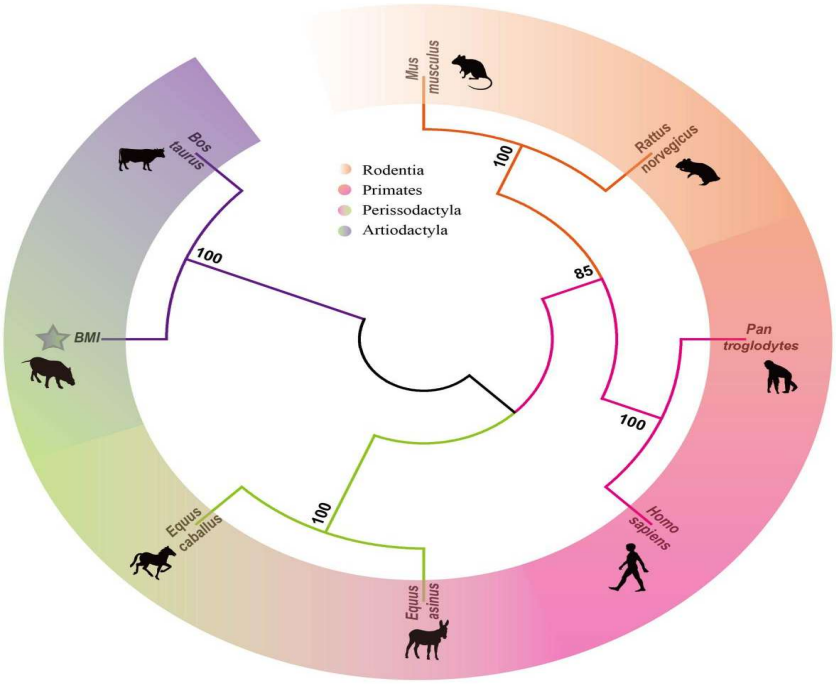


Figure 4. Multi-species phylogenetic tree

ICAM2 protein interaction network analysis: Protein interaction network analysis showed that porcine ICAM2 may interact with 10 proteins, including ICAM1, PECAM1, ITGAL, ITGAM, ICAM3, CD209, ITGB2, RDX, MSN and VCAM1. Among them, ICAM1, ITGAL, ICAM3, ITGB2 and MSN proteins interact most closely (Figure 5).

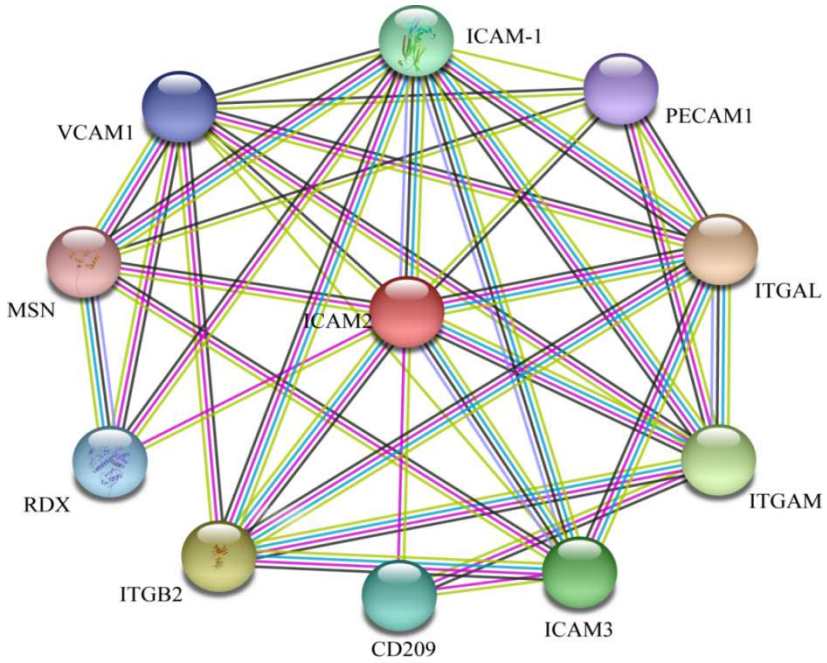


Figure 5. Interacting network of pig ICAM2 protein

The line indicates the confidence of interactions among proteins, and more lines indicates higher confidence.

***ICAM2* expression profiles in different tissues:** The qRT-PCR was performed to determine the expression of pig *ICAM2* in all examined tissues. *ICAM2* mRNA was most highly expressed in the liver, it was highly expressed in the spleen, lymph nodes and tonsils, as well as its expression level was significantly higher than that in other tissues ($P < 0.01$) (Figure 6).

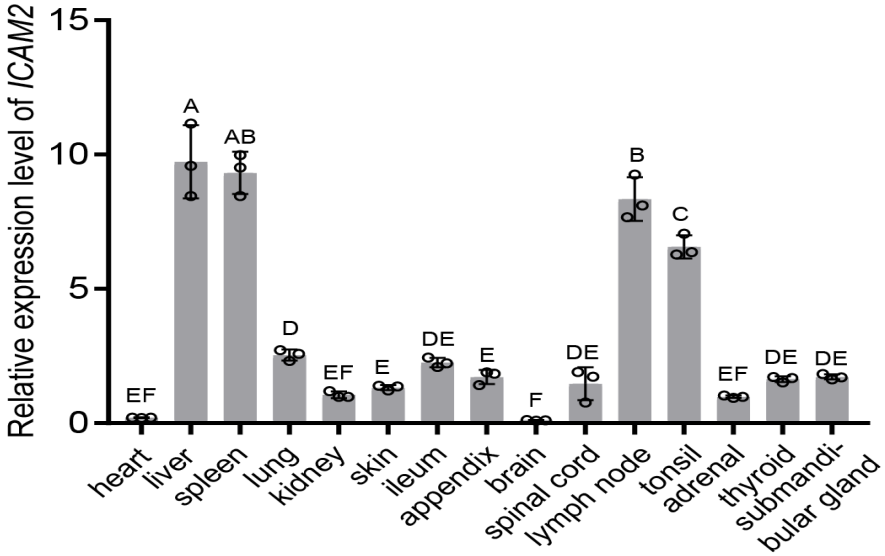


Figure 6. The mRNA expression pattern of *ICAM2* in different tissues

The housekeeping gene *GAPDH* was used as an internal standard. The data are expressed as mean±SE. Different uppercase letters represent highly significantly differences ($P < 0.01$).

The subcellular localization of *ICAM2* in PK15 cells: Porcine testicular PK15 cells were transfected with pEGFP-C1-*ICAM2* plasmid for transient expression. After 24 h of expression, green fluorescence was visible. Cells were then stained with MitoTracker Red CMXRos and Hoechst33342 and observed under an inverted fluorescent microscope. As shown in Figure 7: the green fluorescence is mainly concentrated in the cytoplasm. In order to further analyze the localization of ICAM2 protein in cells, we used software to superimpose the green fluorescence and red fluorescence, and the green fluorescence and blue fluorescence in the same field of view. It can be seen that the green fluorescence and the red fluorescence overlap, It shows that the expression product of *ICAM2* gene in eukaryotes is mainly located in the cytoplasm (Figure 7).

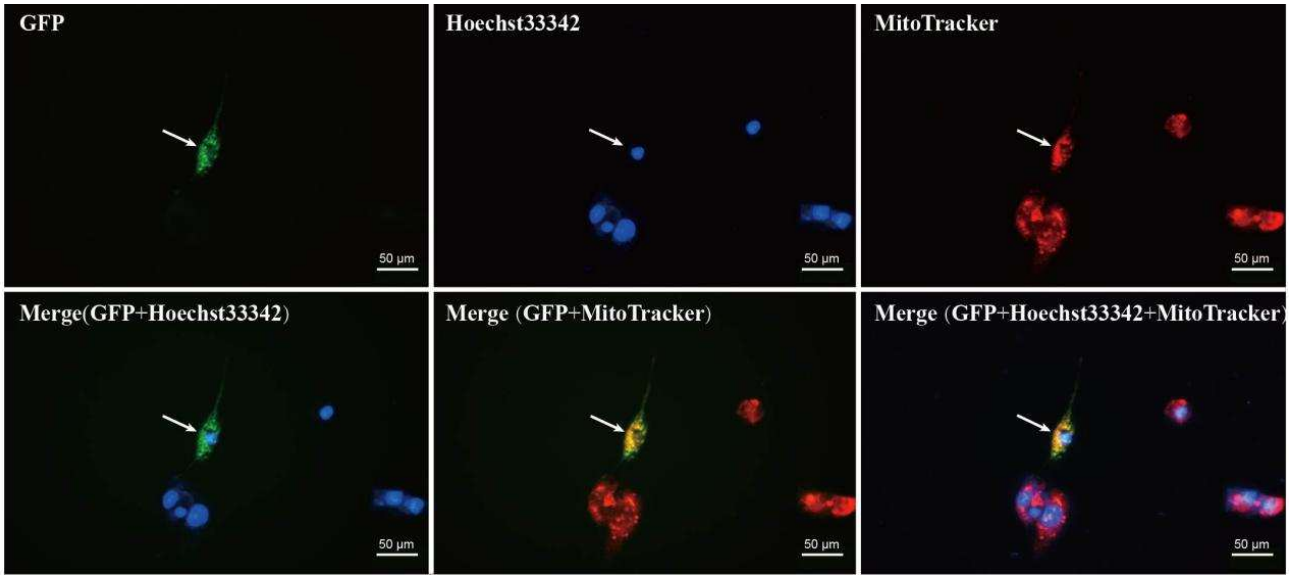


Figure 7. The subcellular location of ICAM2 protein in PK15 cells

DISCUSSION

In xenotransplantation, the donor and recipient come from different species, therefore the genetic differences between them tend to be greater, which led to a stronger immune rejection reaction. The existence and expression level of immune rejection genes directly affect the success rate of xenotransplantation and the survival time of the transplanted organs and can provide important guidance for anti-rejection treatment. This study investigated the sequence characteristics and expression of the porcine *ICAM2* gene and found that the gene is highly conserved and interacts with multiple important proteins. It is noteworthy that there is a signal peptide at the N-terminus of the amino acid sequence of *ICAM2*.

As an illustration, in the activation of T cells, protein signal peptides have the capability to bind to T cell receptors. This binding event initiates the opening of calcium ion channels, subsequently fostering T cell proliferation and differentiation (Pulkina *et al*. 2023). On the other hand, protein signal peptides also have the effect of directly killing pathogenic microorganisms. Some protein signal peptides can penetrate the cell membrane of pathogenic microorganisms and form pores, causing the cell membrane of pathogenic microorganisms to be damaged and die(Chen *et al*. 2020). The investigation revealed that the N-terminal amino acid sequence of ICAM2 spanning pre-1-23 AA functions as a signal peptide. This finding implies a potential pivotal role for this sequence in modulating immune responses.

The *ICAM2*, by itself, is insufficient to ensure the proper progression of the organism's immune-inflammatory response. Effective participation in these processes necessitates collaboration between ICAM2 and other proteins. The analysis of protein-protein interactions revealed that ICAM2 has the potential to interact with 10 different proteins, including ICAM1, PECAM1, ITGAL, ITGAM, ICAM3, CD209, ITGB2, RDX, MSN and VCAM1. A family of membrane molecules, collectively known as cell adhesion molecules (CAMs), is essential for the migration of leukocytes from the blood to inflamed tissues (Vainer 1997). In the process of cell movement, different CAMs are assigned to different stages, and members of this family include ICAM1, ICAM2, ICAM3. Soluble ICAM1, a adhesion molecule released into circulation, possesses immunomodulatory potential and is regarded as both a diagnostic and prognostic marker in numerous inflammatory diseases (Palmer *et al*. 2002). *ICAM1* is recognized as a key site of inflammation that facilitates lymphocyte migration and entry into the lung (Lehmann *et al*. 2003). Both ICAM-2 and ICAM-3 are expressed on

endothelial cells and serve as receptors for the integrin LFA-1 during lymphocyte and dendritic cell trafficking (Van Kooyk and Geijtenbeek 2002). The migration of endothelial cells is mainly accomplished through the interaction of PECAM1 on endothelial cells and leukocytes (Piali *et al*. 1995). Furthermore, PECAM-1 and ICAM1 may be further involved in the migration of leukocytes across the connective tissue of the intestinal lamina propria, and may also be involved in the interaction between leukocytes and epithelial cells (Meenan *et al*. 1996). DC-SIGN serves as the primary receptor for dengue infection. DC-SIGN, also known as CD209, is expressed on dendritic cells (DCs) in combination with ICAM-3, which is expressed on T cells to facilitate the initial interaction between DCs and T cells (Wang *et al*. 2011). Integrin alpha L (ITGAL), a member of the integrin family, is expressed in immune cells and plays a primary role in regulating intercellular adhesion as well as providing costimulatory signals for lymphocytes (Kuwano *et al*. 2010; Sammarco *et al*. 2018). The mentioned protein holds a crucial role in angiogenesis and cancer development, and it is also intricately involved in immune responses and inflammatory processes (Seguin *et al*. 2015). ITGB2 and ITGAM exhibit tissue-specific expression in the bone marrow (Uhlén *et al*., 2015). ITGB2 is particularly implicated in leukocyte adhesion, migration, and immune responses, including the induction of cytotoxicity by natural killer (NK) cells (Wang *et al*. 2021). ITGAM and ITGB2 are upregulated in myeloma and are involved in cytokine-receptor interactions, innate immune responses, and inflammatory responses (Bi *et al*. 2022). In addition, the integrin ITGAM/ITGB2, which is related to immunity and inflammation, is gradually increased in mice with the differentiation of hematopoietic stem cells (Herb *et al*. 2018). The RDX gene encodes a radioactive protein, and mutations in the gene cause hearing loss (Khan *et al*. 2007). MSN have attracted extensive attention due to their high potential for targeted drug delivery. It has been found that functionalized silica nanoparticles are rapidly and efficiently taken up by specialized antigen-presenting cells, such as dendritic cells, into the endosomal compartment. MSN induce immune responses by activating markers and pro-inflammatory cytokines (Heidegger *et al*. 2016). VCAM-1 (Vascular cell adhesion molecule-1) is expressed on both the luminal and lateral surfaces of endothelial cells during inflammatory conditions. Its function involves mediating the rolling and adhesion of various leukocyte subsets, acting as a prerequisite for their recruitment from the bloodstream into tissues (Wittchen, 2009).

The distribution of *ICAM2* is relatively limited, mainly expressed in vascular endothelial cells, lymphocytes, monocytes, megakaryocytes and platelets (de Fougerolles *et al*. 1991). The study revealed that *ICAM2* mRNA exhibits the highest expression in the liver, with elevated expression levels observed in tissues such as the spleen, lymph nodes, and tonsils. Notably, its expression was significantly higher than that in the other 11 tissues ($P < 0.01$). This observation indicates that the expression levels of *ICAM2* are higher in immune-related tissues, aligning with previous research findings. Subsequent investigations into subcellular localization have unveiled the predominant presence of ICAM2 in the cytoplasm. In summary, the identification of these protein interactions with ICAM2 provides valuable insights and potential avenues for further research, enhancing our understanding of the function and molecular mechanisms of *ICAM2* in BMI.

Conclusion: The full-length CDS of the *ICAM2* gene in the Banna minipig inbred line was obtained. The amino acid sequence and structural features of the gene were analyzed to construct a protein-protein interaction network. This study can lay the foundation for further research on the function of *ICAM2* gene in BMI, and also to further explore the adverse reactions during xenotransplantation, especially immune rejection.

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Authors' contributions: J.L. Huo conceived the study and participated in its design and coordination. X. Zhang drafted the first draft and H.L. Huo revised it. X. Zhang participated in the laboratory work and completed protein extraction and cell culture with the help of Y.Y.Chen. J.L. Huo directed the project. All authors have read and approved the final version of the manuscript.

Conflict of interest declaration: No potential conflict of interest was reported by the authors.

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