

*Qi Ren and Tong Li contributed equally to this work and share first authorship

RBCs of Asian-type DEL do not undergo antibody-mediated phagocytosis by macrophages

Qi Ren^{1,2,3*}, Tong Li^{4*}, Ziyue Mi^{1,2}, Yudi Xie^{1,2}, Lushu Cao⁵, Yan Xia⁵, Haixia Xu^{1,2}, Honghong He⁶, Li Tian^{1,2}, Zhong Liu^{1,2}



¹Clinical Transfusion Research Center, Institute of Blood Transfusion, Chinese Academy of Medical Sciences and Peking Union Medical College, Chengdu, Sichuan Province, China;

²Key Laboratory of Transfusion Adverse Reactions, CAMS, Chengdu, Sichuan Province, China;

³Zhongsan Central Blood Station, Zhongshan, Guangdong Province, China;

⁴Department of Neurosurgery, Pengzhou Second People's Hospital, Chengdu, Sichuan Province, China;

⁵Yaan Center Blood Station, Yaan, Sichuan Province, China;

⁶Department of Blood Screening, Suzhou Blood Center, Suzhou, Jiangsu Province, China

Background - In the Rhesus (Rh) blood group system, D is the most immunogenic antigen. RhD-negative patients with anti-D must be transfused RhD-negative red blood cells (RBC) to avoid hemolytic transfusion. RBC of Asian-type DEL phenotype are typed as RhD-negative by routine blood group serological methods because they have very weak expression of D antigen. The prevalence of Asian-type DEL phenotypes was 30% in RhD-negative Chinese donors. Therefore, this DEL type can be transfused to RhD-negative patients with anti-D. However, there is a lack of direct evidence regarding the safety of this practice and potential mechanisms in act.

Materials and methods - The proportion of Asian-type DEL donors that serologically tested RhD-negative was investigated by using genotyping. Furthermore, a model system for in vivo clearance was established to assess antibody-mediated phagocytosis of Asian-type DEL RBC by macrophages.

Results - We identified six serologically RhD-negative donors, 16 Asian-type DEL donors according to polymerase chain reaction polymerase chain reaction with sequence-specific primers (PCR-SSP), and six PCR-SSP RhD-positive donors across various regions in China. Our study revealed that antibody-mediated RBC clearance was not observed following co-culture of opsonized Asian-type DEL RBC with macrophages.

Discussion - Incompatible transfusion of Asian-type DEL RBC may not result in significant RBC clearance.

Keywords: Asian-type DEL, D antigens, opsonization, phagocytosis, transfusion medicine.

INTRODUCTION

The Rhesus (Rh) blood grouping system is highly polymorphic and immunogenic. D-antigen has greater immunogenicity than almost all other antigens associated with this system¹. In 1984, Okubo and colleagues detected a small amount of D-antigen on the surface of RhD-negative red blood cells (RBC), with the adsorption-elution method. The phenotype of these RBC was called DEL (D eluate)². DEL phenotypes are rare in Caucasian³ and have not been reported in African populations⁴. However, in Asian populations, the prevalence of the DEL variant is 13% in Koreans⁵ and ranged from 2.4% to 32.6% in Chinese⁶ among apparently RhD-negative people. The most common DEL allele in East Asian

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Correspondence: Li Tian
e-mail: 241775291@qq.com



populations is *RHD*DEL1* (*RHD* c.1227G>A) allele^{7,8}. This allele was, therefore, also called Asian-type DEL⁹.

Currently, the RhD phenotype is primarily determined using serological assays. In cases in which both the initial screening and confirmatory tests for RhD antigens yield negative results, the sample is classified as RhD-negative. Since the DEL phenotype cannot be detected by standard serology, DEL RBC are often misidentified as RhD-negative¹⁰. In global transfusion practice, individuals with this phenotype are typically managed as RhD-negative recipients¹¹, resulting in the RhD-negative blood inventory being mixed with DEL-type blood. Alloimmunization against the RhD antigen in RhD-negative individuals can lead to significant transfusion reactions and hemolytic disease of the fetus and newborn¹²⁻¹⁵. Since the molecular basis of the DEL phenotype was first elucidated in 2001, the appropriate transfusion management strategy for individuals with the Asian-type DEL phenotype has been a subject of ongoing debate^{6,16}. It is not yet clear whether the transfusion of Asian-type DEL RBC to RhD-negative recipients with D-antibody will lead to a hemolytic reaction. Therefore, due to the limitations of molecular test methods, there may be a waste of blood resources. The monocyte monolayer assay (MMA) has been effectively used to predict the immune-mediated destruction of antibody-bound RBC in cases involving the transfusion of serologically incompatible blood^{17,18}. For this purpose, a flow cytometry-based fully *in vitro* detection method was applied to directly compare the differences in RBC clearance among subjects with various RhD phenotypes. Monocyte-derived macrophages were used to study the phagocytosis of Asian-type DEL RBC that had been opsonized with a polyclonal anti-D antibody.

MATERIALS AND METHODS

Human samples

EDTA-anticoagulated peripheral whole blood samples from RhD-negative donors collected over a 15-month period at Yaan Blood Center were included. Fresh whole blood samples from donors were obtained after genotyping in order to determine specific RhD expression and phagocytosis of differently opsonized Rh DEL RBC. Additionally, after receiving written informed consent from anonymous healthy individuals, blood samples were collected from them to isolate monocytes.

Serology

The tube method was used to determine the presence of RhD antigen with an anti-D monoclonal (IgG + IgM) reagent (Beijing Kinghawk Pharmaceutical Co., Ltd, Beijing, China). An indirect antiglobulin test was done by a standard tube technique with three anti-D reagents: monoclonal anti-D reagent (CE-Immundiagnostika GmbH, Bensheim Germany); anti-D (Brother Biotech, Changchun, China); and anti-D (Rapid Labs Ltd., Ipswich, UK). Samples which did not react with these reagents were confirmed as serologically RhD-negative. Over 15 months, serologically RhD-negative blood was collected from 114 subjects and further tested for the presence of variant *RHD* alleles by polymerase chain reaction with sequence-specific primers (PCR-SSP).

RHD gene analysis

Genomic DNA was extracted from RhD-negative samples using DNA extraction kits (Promega, Madison, WI, USA). The *RHD* deletion and *RHD*DEL1* (hemizygote) allele were determined by PCR-SSP. *RHD* exons 1-10 were sequenced on an AB3730 sequencer using the BigDye Terminator v3.1 cycle sequencing kit (ThermoFisher Scientific, Waltham, MA, USA) when *RHD* genes were found in samples that could not be explained by the PCR-SSP method. The primers and conditions for PCR were the same as those described previously¹⁹.

Over 15 months, 114 serologically RhD-negative blood samples were collected and further tested for the presence of variant *RHD* alleles by PCR-SSP. Of these 114 samples, 86 (75.4%) were confirmed to be RhD-negative, 21 (18.4%) were found to be DEL and seven (6.2%) cases were reported as "possible D". Of the 86 donors who were initially screened as true RhD-negatives, 14 cases of *RHD*O1N.04* were observed and 72 had both *RHD* deletions according to the genotyping method. The 21 (18.4%) DEL cases were all hemizygous for *RHD*(c.1227G>A). Seven cases underwent further characterization by DNA sequencing which revealed six homozygous for *RHD*(c.1227G>A) and one hemizygous for *RHD*(c.3G>A), both considered DEL by the International Society of Blood Transfusion. Rh phenotyping showed 28 (24.6%) DEL and 86 (75.4%) RhD-negative individuals among the serologically RhD-negative blood donors. We collected 16 DEL samples from donors based on the results of the genotyping experiments. For negative controls, six samples from

donors who had previously been tested negative were collected. Six samples from apparently healthy individuals who were serologically positive were used as positive controls. All samples were obtained from donors with their informed consent.

Red blood cell isolation and opsonization

EDTA-anticoagulated peripheral whole blood samples were collected from healthy individuals or donors with RhD-positive, DEL or RhD-negative phenotypes. The samples were centrifuged at $2,000g$ for 5 min, and washed with phosphate-buffered saline (PBS; Hyclone, Logan, UT, USA). Next RBC (1 mL ; 5×10^8 cells) were isolated and labeled with $5\text{ }\mu\text{L}$ of 10 mM carboxy-fluorescein diacetate succinimidyl ester (CFSE; Absin, China), a cell tracker,

for 15 minutes in PBS at room temperature, and then opsonized with $1,500\text{ IU/mL}$ human anti-D polyclonal antibody (Grifols, Los Angeles, CA, USA). After 1 hour of opsonization at 37°C , the RBC were washed twice using 2% fetal bovine serum (FBS; ExCell Bio, Montevideo, Uruguay) + PBS.

Phagocytosis assay using microscopy and flow cytometry

Macrophage phagocytic capacity was measured using an assay in which RhD-positive RBC, opsonized with polyclonal human anti-D IgG, served as targets. An EasySep™ Human Monocyte Isolation kit (StemCell Technologies, Vancouver, BC, Canada) was used to isolate monocytes from peripheral blood mononuclear cells.

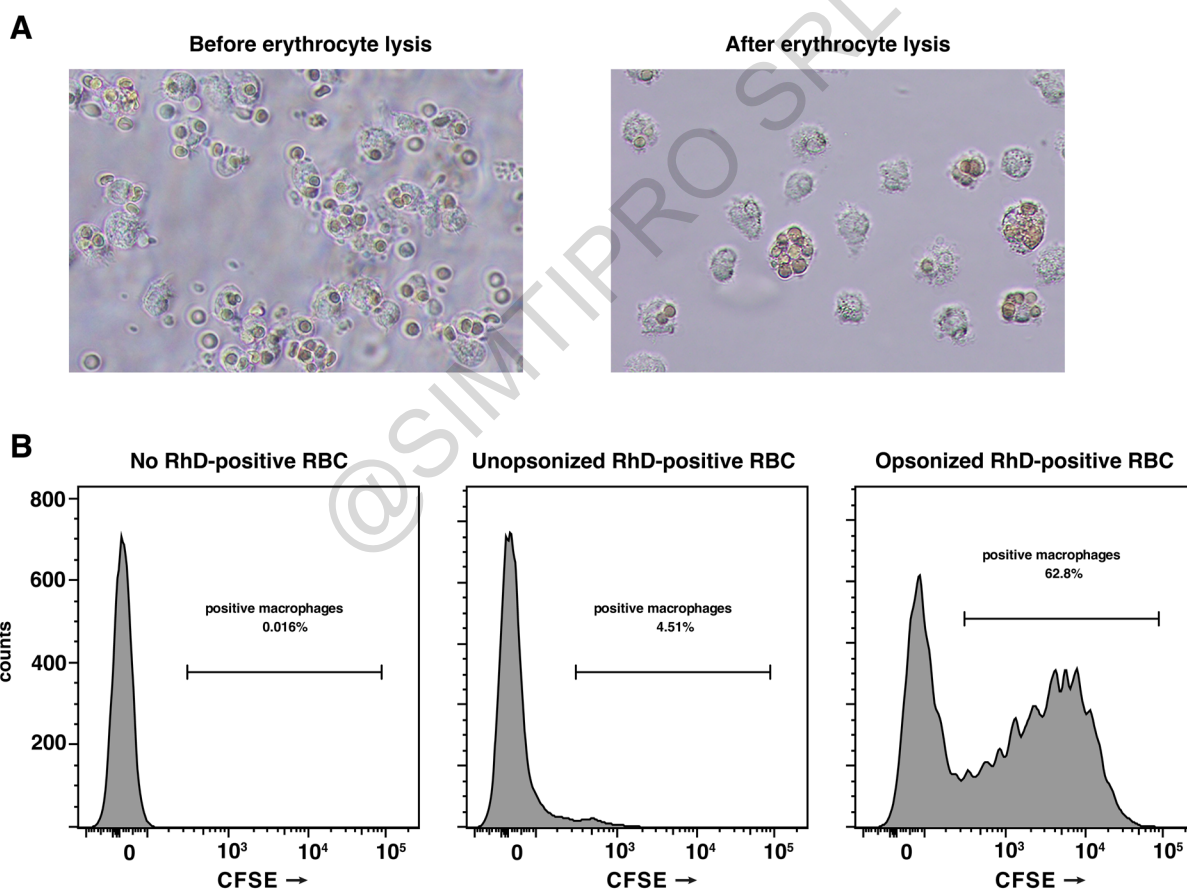


Figure 1 - Macrophages phagocytose anti-D opsonized red blood cells

(A) Monocyte-derived macrophages were co-cultured with RhD-positive red blood cells (RBC) opsonized by anti-D. The left panel is a microscopy image before lysis of RBC. The right panel is a microscopy image after lysis of RBC. (B) Images of flow cytometry quantification of phagocytosis. Macrophages were incubated with unopsonized or anti-D opsonized CFSE-labeled RhD-positive erythrocytes. The percentages represent the numbers of macrophages that were CFSE-positive compared to the total macrophage population. CFSE: carboxy-fluorescein diacetate succinimidyl ester; RBC: red blood cells.

It was confirmed by flow cytometry that these monocytes were >90% pure. Cells were cultured in a 12-well (1×10^6 cells/well) plate (ThermoFisher Scientific) to macrophages with 50 ng/mL macrophage

colony-stimulating factor (Human Recombinant M-CSF, StemCell Technologies) in ImmunoCult™-ST Macrophage medium (StemCell Technologies) at 37°C in 5% CO₂ for 5-7 days. Subsequently, macrophages were incubated

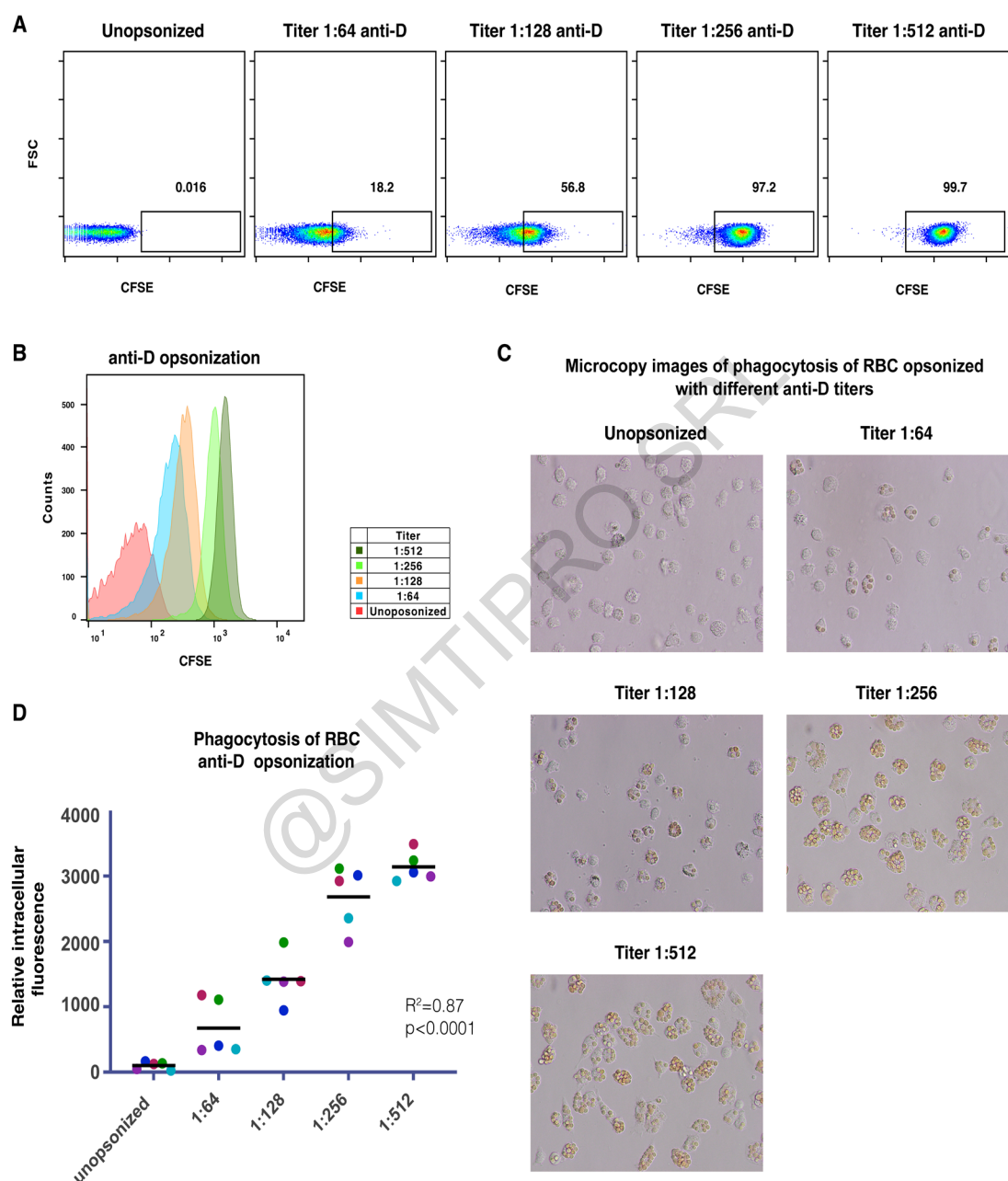


Figure 2 - The level of antibody opsonization correlates with the level of antibody-mediated phagocytosis of red blood cells by macrophages

Red blood cells (RBC) from healthy individuals were incubated with anti-D in increasing titers (1:64, 1:128, 1:256 and 1:512). Unopsonized RBC (left) were used as negative controls. (A, B) Representative plots of five independent experiments are shown. RBC were incubated with macrophages. (C, D) RBC phagocytosis was quantified. A Pearson correlation test was used to assess the correlation between the degree of opsonization of RBC and removal of the RBC by macrophages. CFSE: carboxy-fluorescein diacetate succinimidyl ester; RBC: red blood cells.

for 2 hours at 37°C with opsonized RBC at a ratio of 10 erythrocytes to 1 macrophage. Isotonic ammonium chloride lysing buffer (BD Pharm Lyse™, Franklin Lakes, NJ, USA) was used to lyse non-phagocytosed RBC twice at room temperature for 5 minutes. The lysis buffer was removed using PBS (Hyclone), and microscopy pictures were taken using an Olympus microscope (Hachioji, Japan). The macrophages were then washed again in 2% FBS+PBS. The macrophages' ingestion of CFSE-labeled RBC (including 6 DEL, 6 RhD-negative and 16 RhD-negative positive samples) was quantified using flow cytometry with the FlowJo™ 10 application (FlowJo LLC, Ashland, OR, USA).

Statistical analysis

All statistical analyses and graphical presentation were conducted using GraphPad Prism 9.0. Kruskal-Wallis tests were used to compare D-antigen expression levels of RBC and levels of anti-D-mediated phagocytosis. Correlations between D antigen expression on RBC as well as RBC opsonization and phagocytosis were calculated using a Pearson's correlation test. *p*-values <0.05 were considered statistically significant.

RESULTS

Macrophages phagocytose red blood cells opsonized by human anti-D IgG

When anti-D-opsonized RBC are incubated at 37°C with macrophages, they bind and undergo phagocytosis. Extracellular not ingested erythrocytes were lysed to differentiate phagocytosis from binding (Figure 1A). A flow cytometry assay was used to quantify phagocytosis by labeling RBC with CFSE and detecting macrophage uptake of RBC. An example is shown in Figure 1B, in which macrophages in the absence of anti-D bound 4.51% of the RBC target, with this value increasing to 62.8% in the presence of 1:128 anti-D (Figure 1B).

Antibody opsonization and phagocytosis

The effect of antibody titer on phagocytosis of RhD-positive RBC by macrophages was studied. RBC were incubated with increasing titers of anti-D (1:64, 1:128, 1:256 and 1:512), resulting in increased opsonization (Figure 2A, B). Specific phagocytosis of RhD-positive RBC by macrophages was enhanced by the increased opsonized RBC. The strength with which the antibody bound the D-antigen of RhD-positive RBC

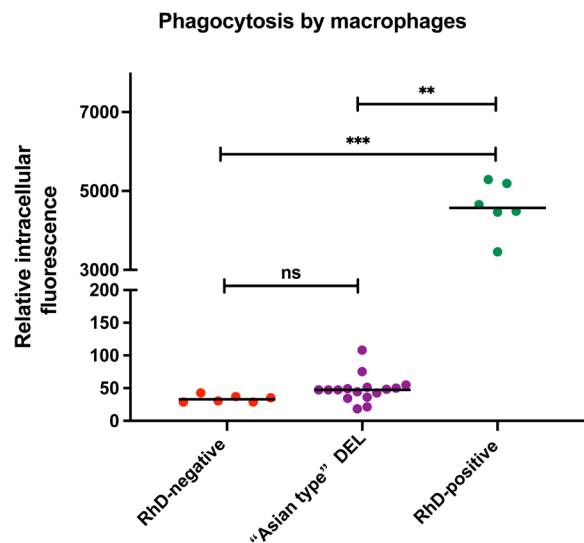


Figure 3 - Opsonization of red blood cells obtained from healthy individuals with RhD-negative and Asian-type DEL does not lead to antibody-mediated phagocytosis by macrophages

RhD-positive red blood cells (No.=6), Asian-type DEL (No.=16), or RhD-negative (No.=6) were all opsonized with anti-D, and phagocytosis by macrophages was determined. The statistical differences in phagocytosis were determined using a Kruskal-Wallis test (RhD-negative, Asian-type DEL, RhD-positive). ns: not significant; ***p*<0.01, ****p*<0.001.

was correlated with RBC removal by macrophages ($r^2=0.87$) (Figure 2C, D).

Antibody-mediated Asian-type DEL red blood cell phagocytosis by macrophages

Subsequently, in order to identify the phagocytosis of cells with different RhD phenotypes by macrophages, RBC from donors with RhD-positive, negative or DEL were obtained and opsonized with the relevant human anti-D at a saturating titer. Compared with the unopsonized control, phagocytosis of anti-D opsonized RhD-positive RBC was significantly increased, whereas this was not observed for RBC obtained from donors with Asian-type DEL (Figure 3).

DISCUSSION

The complex formed by the binding of IgG antibodies to RBC antigens is recognized by specific macrophage receptors, facilitating the phagocytosis of opsonized RBC. The monocyte-monolayer assay is a well-established and widely used technique employed to predict immune-mediated RBC destruction by quantifying the

rate of *in vitro* phagocytosis of antibody-bound RBC by monocytes^{17,18,20}. In our experiment, we employed allogeneic monocyte-derived macrophages due to the requirement for freshly drawn blood, a method demonstrated to be effective in previous studies²¹⁻²³.

Recent results in mice suggest that antigen density can dictate the consequence of antibody-mediated RBC clearance²⁴. However, the expression of RhD antigen on the surface of Asian-type DEL is very low, with less than 22 D antigen sites²⁵. It is unknown whether a hemolytic transfusion reaction will occur when the antigen density is below a certain threshold. Using the macrophage model system outlined in the present study, Asian-type DEL appears not to lead to antibody-mediated phagocytosis of RBC by macrophages. The lack of phagocytosis of DEL RBC could have significant implications in terms of transfusion medicine. It could be valuable to discuss how this might affect blood availability or safety, particularly in populations in which DEL phenotypes are prevalent.

The DEL samples in this study were identified by PCR-SSP genotyping and DNA sequencing. It can, therefore, be concluded that Asian-type DEL RBC are not phagocytosed and a relationship cannot be drawn between antibody-mediated erythrocyte clearance and antigen density. According to the results, it can be speculated that the DEL RBC antigen expression is below the threshold that can lead to the occurrence of a hemolytic transfusion reaction.

A clinical trial by Shao *et al.* indicated that none of the patients with anti-D antibodies experienced an acute hemolytic episode following transfusions with Asian-type DEL RBC²⁶. In our study, DEL RBC opsonized with anti-D were co-cultured with macrophages, and no RBC removal was observed. However, in the study by Shao *et al.*²⁶, three patients had a pre-existing anti-D and were transfused with DEL-positive RBC. Two patients had a perceived drop in hemoglobin (titers of 8), and one patient did not (titer 512). This suggests that transfusions of Asian-type DEL RBC to anti-D positive recipients may provoke a post-transfusion hemolytic episode, potentially impacting the safety of transfusion in recipients to a certain extent. There are several possible explanations for why our work does not support the conclusion of Shao *et al.* The first potential explanation is related to the observational study design, which creates

potential for confounding and bias that may influence the results. It is difficult to prove the ineffectiveness of RBC transfusion and that the occurrence of hemolysis is due to transfusion of DEL RBC. Meanwhile, the mechanism of immune RBC destruction should be considered. The clinically significant phagocytosis by monocytes might merely be one of the mechanisms of immune RBC destruction. The ways in which macrophages affect erythrocyte hemolysis include not only RBC engulfment and destruction inside the macrophages, but also some other ways such as RBC remaining outside of macrophages and being lysed by antibody-dependent cell-mediated cytotoxicity²⁷. Furthermore, besides macrophages, there are other immune cells involved in hemolysis, for example, granulocyte phagocytosis²⁸ and natural killer cells²⁹.

In this study, some attempt was made to provide experimental evidence of the possibility of hemolysis in true RhD-negative patients with alloanti-D after transfusion of Asian-type DEL RBC, but the limited *in vitro* experimental data are indirect. Hemolysis involves not only extravascular hemolysis, but also intravascular hemolysis although anti-D do not commonly result in intravascular hemolysis. Consequently, more rigorous clinical trials need to be conducted to prove whether the infusion of DEL RBC to RhD-negative recipients with anti-D will induce hemolysis *in vivo*.

In summary, our data demonstrate that phagocytosis by macrophages is not significantly different between opsonized Asian-type DEL and RhD-negative RBC by anti-D and suggest that no phagocytosis was observed in Asian-type DEL RBC opsonized by anti-D human alloantibodies. This finding implies that RhD-negative patients with anti-D might tolerate DEL+ RBC transfusions without significant hemolysis or transfusion reaction.

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Authors' contributions

LT and ZL designed the study. QR, YX, ZM, and HX conducted experiments. LT and HH acquired data.

TL analyzed data. QR wrote, reviewed, and edited the manuscript. All Authors read and approved the final version of the manuscript.

The Authors declare no conflicts of interest.

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