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Human kidney anion exchanger 1 interacts with kinesin family member 3B (KIF3B)

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ABSTRACT

Impaired trafficking of human kidney anion exchanger 1 (kAE1) to the basolateral membrane of α-intercalated cells of the kidney collecting duct leads to the defect of the Cl^-/HCO_3^- exchange and the failure of proton (H^+) secretion at the apical membrane of these cells, causing distal renal tubular acidosis (dRTA). In the sorting process, kAE1 interacts with AP-1 mu1A, a subunit of AP-1A adaptor complex. However, it is not known whether kAE1 interacts with motor proteins in its trafficking process to the plasma membrane or not. We report here that kAE1 interacts with kinesin family member 3B (KIF3B) in kidney cells and a dileucine motif at the carboxyl terminus of kAE1 contributes to this interaction. We have also demonstrated that kAE1 co-localizes with KIF3B in human kidney tissues and the suppression of endogenous KIF3B in HEK293T cells by small interfering RNA (siRNA) decreases membrane localization of kAE1 but increases its intracellular accumulation. All results suggest that KIF3B is involved in the trafficking of kAE1 to the plasma membrane of human kidney α-intercalated cells.

1. Introduction

Human anion exchanger 1 (AE1 or band 3) is a chloride and bicarbonate exchanger (Cl^-/HCO_3^-) which is involved in maintaining acid–base homeostasis in the human body [1]. Two isoforms of AE1, erythroid AE1 (eAE1) and kidney AE1 (kAE1) are encoded by *solute carrier family 4, member 1* (*SLC4A1*) gene (MIM 109270). Transcription of eAE1 in the erythroid precursor is under the control of the erythroid-specific promoter upstream of exon 1, whereas the renal transcription arises from the distinct promoter within intron 3 of the *SLC4A1* gene [2]. Thus, the kAE1 polypeptide lacks 65 amino acids presented at the N-terminus of human eAE1 [3]. kAE1, which is the basolateral Cl^-/HCO_3^- exchanger of the acid-secreting α-intercalated cells of kidney distal tubule [4], comprises 846 amino acids and has three functionally distinct structural domains including a cytoplasmic amino-(N-) terminal domain (403 amino acids), a central transmembrane domain (497 amino acids) and a short cytoplasmic carboxyl-(C-) terminal domain (40 amino acids) [5,6].

Mutations of the *SLC4A1* gene can cause distal renal tubular acidosis (dRTA), which is characterized by the impaired H^+ secretion into urine leading to systemic metabolic acidosis. It has previously shown that dRTA is caused either by preventing the transport of mutant kAE1 to the cell surface or by mis-targeting the mutant kAE1 to the apical membrane instead of the correct basolateral membrane of the α-intercalated cells [7,8]. Deletion of either the N-terminal or C-terminal domain of kAE1 resulted in the apical mis-localization, suggesting that a determinant within the kAE1 N-terminus cooperates with the C-terminus for kAE1 basolateral localization [14]. Despite much evidence suggesting that the C-terminal portion of kAE1 is involved in basolateral membrane trafficking, very little information is known about proteins that physically interact with the C-terminal tail of kAE1 [9]. Our group is interested in identifying the protein that interacts with kAE1 and plays a role in its basolateral trafficking. We have recently reported that AP-1 mu1A, a subunit of AP-1A adaptor complex involving in sorting of the cargo proteins, interacts with the C-terminus of kAE1 [14]. However, it is not known whether or not kAE1 interacts with motor proteins, such as kinesins, which are also important in the trafficking process.

KIF3B is one of the kinesin II subfamilies of the kinesin superfamily, which consists of a large family of molecular motors that transport the intracellular cargo along the microtubules using the energy derived from hydrolysis of ATP [10]. Members of the kinesin II subfamily are plus end-directed motor proteins that are involved in the trafficking, assembly and maintenance of cilia and flagella, and in the transport of the endoplasmic reticulum to the Golgi membrane [11,12]. A heterotrimeric complex of KIF3B with KIF3A and KAP3 determines the functional diversity of the KIF3B complex. Transportation of matrix metalloproteinase (MT1-MMP) vesicles along microtubules is regulated by KIF5B and KIF3A/KIF3B kinesins.

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Results from siRNA-KIF3A/KIF3B knockdown studies revealed that transport by these kinesins is essential for transport of MT1-MMP to the cell surface of the primary human macrophage [13]. In addition, the interaction between KIF3B and chloride channel protein (CLC-5) was previously shown to facilitate the transport of CLC-5-containing vesicles to the cell surface of HEK 293 cells [14].

2. Materials and methods

2.1. Plasmid constructions

PCR-based amplification of KIF3B-HA was performed by using pcDNA3.1-KIF3B-His, which is available in our laboratory as a template and through using primers containing the hemagglutinin (HA) epitope sequences to add HA at the C-terminus of KIF3B. KIF3B-HA was cloned into *Eco*RV and *Xho*I sites of a pcDNA3.1/hygro plasmid. The clone was designated pcDNA3.1-KIF3B-HA. Plasmid pcDNA3/kAE1-Myc, containing a sequence of Myc epitope inserted at position 557 in the third extracellular loop of kAE1, was generated from pcDNA3-kAE1 by site-directed mutagenesis following the protocol of the QuickChange TM site-directed mutagenesis kit from Stratagene, USA. By DNA sequencing, the tag and insert sequences in the plasmid constructs were proved to be correct and in frame with the gene sequences.

2.2. Cell culture and transfection

Human embryonic kidney (HEK293T) cells were grown in DMEM/F-12 (Gibco) supplemented with 10% FBS (Gibco) and 1.2% penicillin/streptomycin in 6-well plates prior to transfection. Cells were transfected using Lipofectamine 2000 (Invitrogen) according to the manufacturer's instructions. Cells were processed for further studies at 48 h post-transfection.

2.3. Co-immunoprecipitation and immunoblotting

HEK293T cells were co-transfected with pcDNA3/kAE1-Myc and pcDNA3.1-KIF3B-HA constructs. Two days after transfection, the transfected cells were detached and collected by centrifugation. Cells were lysed in PBS containing 1% Triton X-100 and inhibitors cocktail (Roche). Aliquots of the cell lysates were saved and the remaining cell lysates were incubated with the mouse anti-Myc antibody followed by precipitation with Protein G-Sepharose (Thermo Scientific). The bound kAE1 protein was eluted with Laemmli buffer before separation by electrophoresis and detection by Western blot analysis using the rabbit anti-HA polyclonal antibody (Invitrogen) as the primary antibody and the swine anti-rabbit IgG-HRP (Santa Cruz) as the secondary antibody. Chemiluminescent signals generated by SuperSignal West Pico Chemiluminescent Substrate (Thermo Scientific) were detected by exposure to an X-ray film.

2.4. GST pull-down assay

The pGEX4T-2-GST, pGEX4T-2-GST-Nt-kAE1 and pGEX4T-2-GST-Ct-kAE1 constructs [14] were transformed into *Escherichia coli* strain BL21 (DE3). The pTrcHisA-KIF3B was transformed into *E. coli* strain DH5α. The bacterial cells were grown in Luria broth to express the recombinant proteins. The bacterial cells were lysed by lysis buffer. The GST or GST-fusion proteins were conjugated with Glutathione-Sepharose 4B beads (Amersham) and then incubated with HEK293T cell lysate. The unbound proteins were eliminated by serial washing as described previously [15]. The binding protein complexes were eluted and subjected to Western blot analysis using the rabbit polyclonal anti-KIF3B antibody (Santa Cruz) as the primary antibody and the swine anti-rabbit IgG-HRP (Santa Cruz) as the secondary antibody. Chemiluminescent signals generated by SuperSignal West Pico Chemiluminescent Substrate (Thermo Scientific) were detected by exposure to an X-ray film.

2.5. RNA interference

Small interfering RNA (siRNA) directed against KIF3B derived from the mRNA sequence (5′-CCT GCA AGG TTT CAA TGG AAC CA-3′) of human KIF3B (siKIF3B) was purchased from Invitrogen. Transfection of either siKIF3B or siControl was performed using Lipofectamine 2000 (Invitrogen). HEK293T cells (5×10^5 cells) were seeded into a six-well plate, 24 h before transfection. For the co-tranfection with knockdown experiment, pcDNA3/kAE1-Myc was transfected after 24 h of siRNA transfection. Cells were harvested 72 h after the siKIF3B transfection.

2.6. Double immunofluorescence staining

HEK293T cells were grown on coverslips for 24 h, co-transfected with plasmid constructs using Lipofectamine 2000 (Invitrogen) and cultured for 48 h. The protocol for double immunofluorescence staining was described previously [16]. Firstly, co-staining of kAE1 and KIF3B was performed by using the mouse anti-Myc and the rabbit anti-KIF3B (Santa Cruz) as the primary antibodies followed by the goat anti-mouse IgG conjugated with Alexa 488 fluoresceine (Molecular Probes) and the donkey anti-rabbit IgG conjugated with Cy3 fluoresceine (Jackson Immunoresearch Laboratories) as the secondary antibodies. Secondly, co-staining of kAE1 and calnexin was performed by using the mouse anti-Myc and the rabbit anti-calnexin (Santa Cruz) as the primary antibodies followed by the goat anti-mouse IgG conjugated with Alexa 488 fluoresceine (Molecular Probes) and the donkey anti-rabbit IgG conjugated with Cy3 fluoresceine (Jackson Immunoresearch Laboratories) as the secondary antibodies.

Human fresh frozen tissues were obtained from leftover specimens of the Department of Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand. The protocol was approved by the Human Research Ethics Committee, Siriraj Institutional Review Board, Mahidol University (#Si128/2011). Sections were fixed by acetone for 10 min before immunostaining with the rabbit anti-Ct-kAE1 and the goat anti-KIF3B (Santa Cruz) as the primary antibodies, followed by the anti-mouse antibody coupled to Cy3 and the anti-rabbit antibody coupled to Alexa 488 as the secondary antibodies. The sections were then examined under the LSM 510 META confocal microscope (Carl Ziess).

2.7. Flow cytometry

Myc epitope was inserted at the third extracellular loop of kAE1 to express extracellularly. As a result, expression of kAE1-Myc on the cell surface could be determined by fluorescence staining and flow cytometry [16]. HEK293T cells were co-transfected either with the pcDNA3/kAE1-Myc and siKIF3B or with the pcDNA3/kAE1-Myc and siControl, respectively. Two days after transfections, the cells were collected and determined by flow cytometry as previously described [16].

3. Results

3.1. kAE1 interacts with KIF3B and dileucine motif of Ct-kAE1 is critical for KIF3B binding

To establish whether kAE1 interacts with KIF3B in kidney cells or not, we performed co-immunoprecipitation and GST pull-down

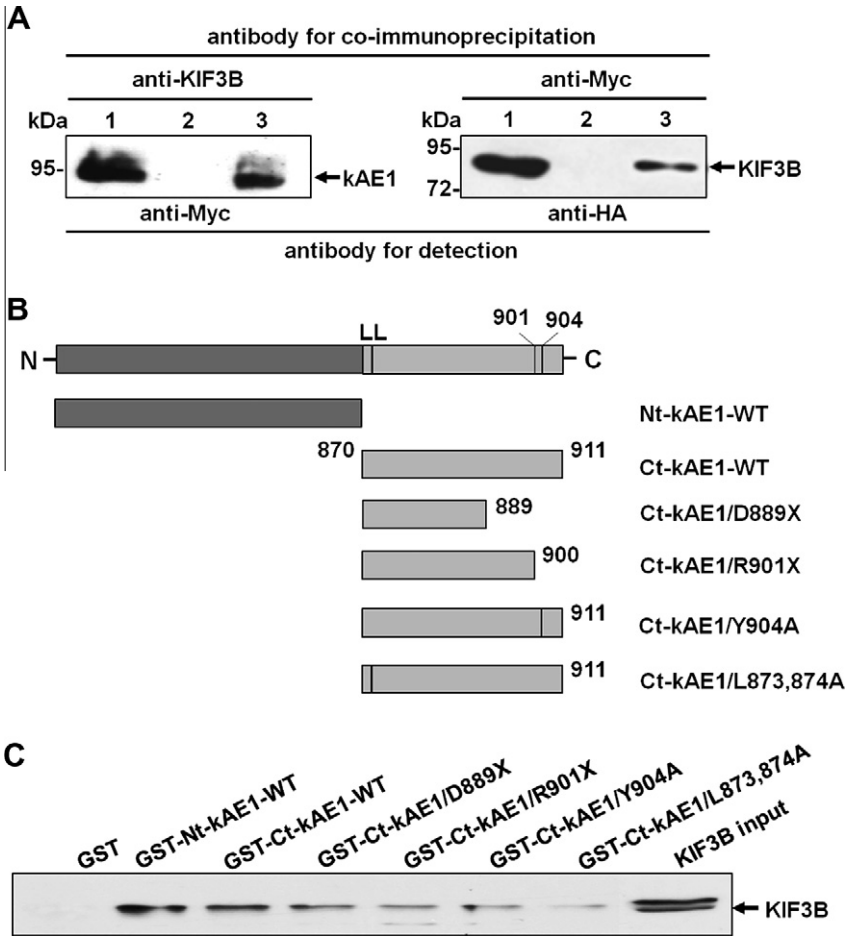

Fig. 1. Interaction of kAE1and KIF3B in HEK293T cells. (A) Co-immunoprecipiation studies using HEK293T cells demonstrated interactions between kAE1 and KIF3B. *Lane 1*: input; *Lane 2*: pull-down with no antibody; *Lane 3*: pull-down with anti-KIF3B (left panel), or anti-HA antibodies (right panel). (B) Maps of the carboxyl terminus of kAE1 (Ct-kAE1). Different GST-Ct-kAE1-mutants were generated from GST-Ct-kAE1-WT. (C) GST pull-down binding assay.

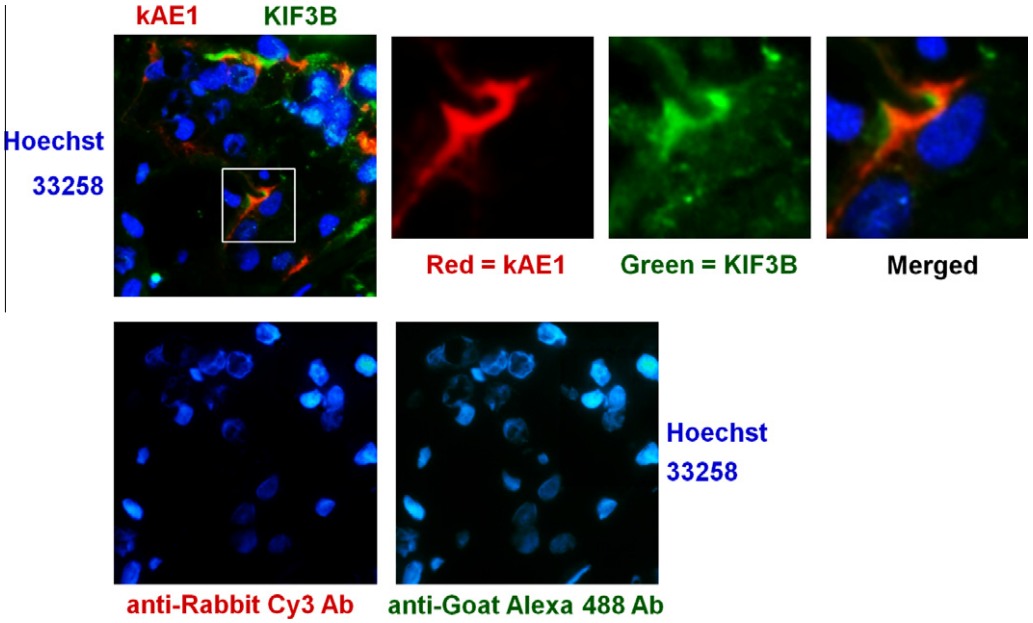

Fig. 2. kAE1 protein co-localizes with endogenous KIF3B in human kidney tissue. Fresh frozen human kidney sections were incubated with the rabbit anti-kAE1 antibody and the goat anti-KIF3B (top panels) or no primary antibody (bottom panels). Slides were then incubated with the anti-rabbit antibody coupled to Cy3 (red) and the anti-goat antibody coupled to Alexa 488 (green), followed by nuclear staining with Hoechst 33,258 (blue). The samples were examined using a LSM 510 META Carl Zeiss confocal microscope and a 100× lens. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

studies. The interaction was analyzed by co-transfection of HEK293T cells with the plasmid constructs expressing kAE1 and KIF3B tagged with Myc and HA epitopes, respectively. When KIF3B-HA was immunoprecipitated with anti-KIF3B antibody, the immunoreactive band of kAE1 was detected in the immunoprecipitate (Fig. 1A, left panel). In addition, kAE1-Myc was reciprocally co-immunoprecipitated with anti-HA antibody (Fig. 1A, right panel). The results indicated the interaction of kAE1 and KIF3B in HEK293T cells.

A series of GST pull-down assays were subsequently performed using Nt-kAE1 and Ct-kAE1 containing truncated or point mutations (Fig. 1B). GST-Nt-kAE1-WT, GST-Ct-kAE1-WT and a series of GST-Ct-kAE1-mutants interacted with KIF3B in the GST pull-down assays (Fig. 1C, lanes 2–6). In contrast, a very faint band was ob – served in the binding between GST-Ct-kAE1/L873, 874A and KIF3B from HEK293T cell lysate (Fig. 1C, lane 7) – suggesting that dileucine motif of Ct-kAE1 is critical for KIF3B binding. As a control, GST alone did not interact with KIF3B (Fig. 1C, lane 1).

3.2. kAE1 co-localizes with KIF3B in human kidney tissue

We further asked whether kAE1 interacts with KIF3B in human kidney tissue or not. Human kidney sections were stained with the rabbit anti-Ct-kAE1 and the goat anti-KIF3B as the primary antibodies followed by the anti-mouse antibody coupled to Cy3 and the anti-rabbit antibody coupled to Alexa 488 as the secondary antibodies (Fig. 2). In contrast with sections incubated with secondary antibodies only (Fig. 2, bottom sections), the antibody against kAE1 detected both a clear predominant basolateral staining and a discrete vesicular intracellular staining. In a high intensity, KIF3B was stained similarly as that of kAE1 at the basolateral membrane. In the insets (Fig. 2, top right boxes), a higher magnification of the intracellular red and green staining showed co-localization of both endogenous kAE1 and endogenous KIF3B, supporting that kAE1 interacts with KIF3B in the human kidney tissue.

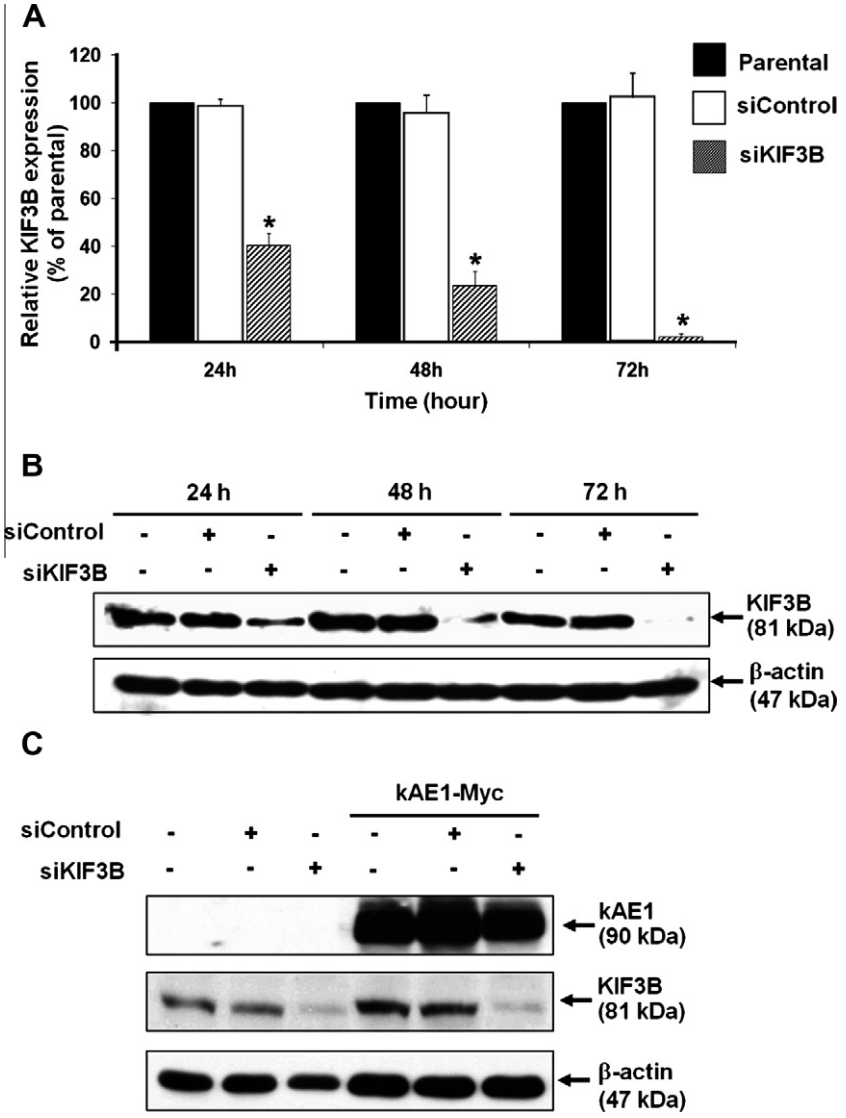

Fig. 3. Endogenous suppression of KIF3B by small interfering RNA (siRNA) in HEK293T cells. (A) Expression of KIF3B mRNA was determined by real-time PCR. Black columns represent the baseline KIF3B expression in HEK293T cells (parental expression, 100%). White columns represent the relative KIF3B expression after transfection with siControl. Strip columns represent the relative KIF3B expression after transfection with siKIF3B. Results are averaged (mean + SE) from three independent experiments. (B) Expression of KIF3B protein was detected by Western blot analysis. (C) Expression of kAE1-Myc after co-transfection with siRNA for 72 h was detected by Western blot analysis.

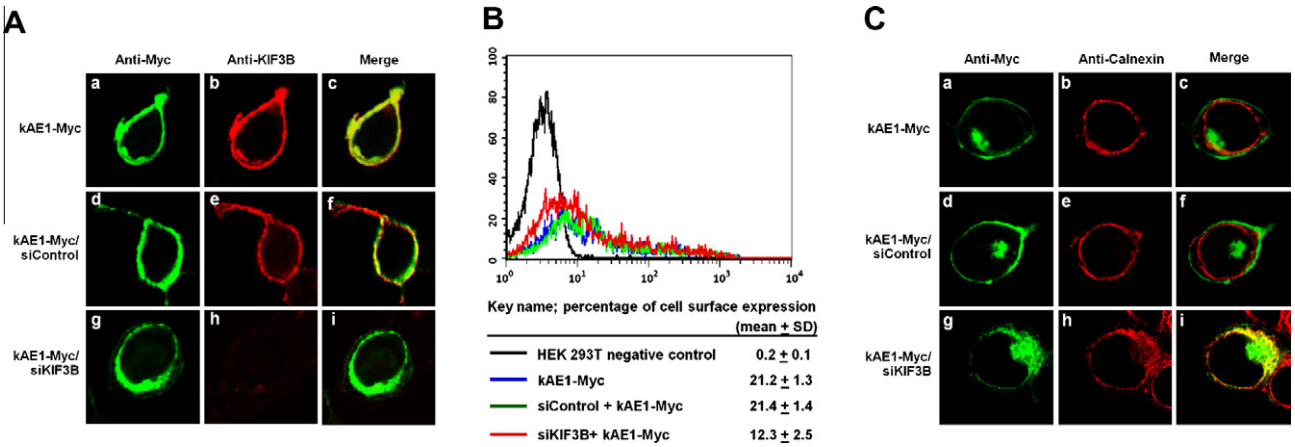

Fig. 4. KIF3B knockdown significantly reduced kAE1 on the membrane and accumulated kAE1 in ER. (A) HEK293T cells were transfected with kAE1-Myc (a–c) and co-transfected with siControl (d–f) or with siKIF3B (g–i). (B) Cell-surface expression of kAE1-Myc in transfected HEK293T cells was measured by flow cytometry. Percentages of cell surface expression of kAE1-Myc (mean ± SD) in different conditions are indicated. (C) Localizations of kAE1 and ER marker were shown in HEK293T cells with suppression of KIF3B by siRNA.

3.3. Knocking-down the expression of endogenous KIF3B by siRNA decreased cell surface kAE thereby accumulating kAE1 in the ER

To study the functional significance of KIF3B, we employed RNAi to transiently deplete the expression of endogenous KIF3B in kAE1-transfected HEK293T cells. The efficiency of the siKIF3B transfection was shown by real-time PCR (Fig. 3A) and immunoblotting (Fig. 3B), respectively. Transfection of HEK293T cells with siKIF3B reduced both KIF3B mRNA and protein >80% within 48 h. To ensure that siKIF3B did not affect kAE1 expression, kAE1 protein expression level was further determined by Western blot analysis. The expression of kAE1-Myc was not changed while that of KIF3B was markedly decreased (Fig. 2C), indicating that an off-target effect of the siKIF3B did not occur.

Sub-cellular localization of kAE1 and KIF3B in HEK293T cells was further examined by immunofluorescence stainings and confocal microscopy. HEK293T cells expressing kAE1-Myc were transfected with either siControl or siKIF3B. The results showed that, without KIF3B suppression, kAE1-Myc was located mainly at the cell surface in the parental and siControl cells (Fig. 4A, a–c and d–f). In contrast, with KIF3B suppression, kAE1-Myc was accumulated mainly in the cytoplasm of the cells (Fig. 4A, g–i).

To quantitatively measure kAE1 expression at the cell surface, the plasmid construct, which can express kAE1 containing Myc epitope at the position 557 in the third extracellular loop of kAE1, was used to allow immunological detection of the protein at the surface of intact cells by flow cytometry. The HEK293T cells individually expressing kAE1-Myc or co-expressing kAE1-Myc with siControl transfection had mean fluorescence intensities of 21.2 ± 1.3% and 21.4 ± 1.4%, respectively. However, HEK293T cells co-expressing kAE1-Myc with suppression of KIF3B showed lower levels of kAE1-Myc on the cell surface (12.3 ± 2.5%) than those of the control cells (Fig. 4B).

To focus on the location of kAE1-Myc with respect to intracellular organelles when KIF3B was suppressed, we next co-transfected kAE1-Myc with siKIF3B in HEK293T cells and stained the HEK293T cells with the antibody to calnexin, which was specific to the ER. In the parental and siControl cells, kAE1-Myc was predominantly expressed at the cell membrane and rarely co-localized with calnexin in ER (Fig. 4C, a–f). In contrast, in the cells with KIF3B suppression by siRNA, kAE1-Myc was accumulated mainly in the ER (Fig. 4C, g–i).

4. Discussion

The protein trafficking pathway is a regulated process and requires specific recognitions between cargo molecules and trafficking machinery to achieve correct targeting of cargo proteins to their destinations. Both apical and basolateral transport have common basic behaviors starting from sorting, which take place at the trans-Golgi network (TGN). Then apical and basolateral vesicles are separately transported to their final destinations thereby fusing with the apical and basolateral plasma membranes, respectively [17].

Several sorting signals for basolateral membranes are known, such as tyrosine and dileucine motifs [18]. Adaptor proteins are known to bind to these motifs and are involved in basolateral sorting. We previously reported the interaction between kAE1 and AP-1 mu1A, a subunit of AP-1A adaptor complex. AP-1 mu1A knockdown showed a marked reduction of kAE1 on the cell membrane and increased its accumulation in ER [15]. Motor proteins are also required for transportation of a cargo protein from TGN to the plasma membranes. This study additionally showed that kAE1 physically interacts with KIF3B. A dileucine motif at the C-terminal kAE1 contributes to its interaction with KIF3B. The involvements of the C-terminal kAE1 in the basolateral trafficking were previously reported [19,20]. Firstly, a 20-bp deletion in exon 20 of *SLC4A1* leading to a mutation that changes alanine to leucine (A > L) at position 888 and a premature termination codon at position 889 (A888L + 889X), which truncates the protein by 23 amino acids, were identified in two affected brothers with dRTA [21]. Secondly, R901X (band 3 Walton) mutation, which is an intragenic 13-bp duplication resulting in a deletion of the last 11 amino acids of AE1, was found to be associated with dominant dRTA in two affected brothers of one family [20–23]. Finally, tyrosine residue at position 904 (Tyr904) is crucial for polarized transport of kAE1 as Y904A or Y904A + V907A mutation caused non-polarized distribution of kAE1 in polarized MDCK cells [20,23]. Similar to the AP-1 mu1A knockdown cells, KIF3B knockdown cells significantly reduced kAE1 on the membrane and accumulated kAE1 in the cytoplasm, particularly in ER of the kidney cells. In conclusion, we characterized the interaction between human kAE1 and KIF3B and demonstrated a role for KIF3B in kAE1 trafficking to the plasma membrane.

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