이학석사 학위논문

혈관신생 촉진 자극이 주피세포 발현 항혈관신생 인자인 KAI1/CD82의 발현에 미치는 영향에 관한 연구

Decrease in KAI1/CD82 expression of mural cells in response to angiogenic stimulus

2017년 2월

서울대학교 의과대학원

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남브니엘

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지도교수 김 효 수

이 논문을 남브니엘 석사학위논문으로 제출함

2016년 10월

서울대학교 대학원
의과대학 줄기세포생물학과
남브니엘

남브니엘의 석사학위논문을 인준함

2017년 1월

위 원 장 신 찬 수 (인)

부 위 원 장 김 효 수 (인)

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Abstract

Decrease in KAI1/CD82 expression of mural cells in response to angiogenic stimulus

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Recent studies have highlighted the role of mural cells and tetraspanin molecules in angiogenesis. We and others [1] previously observed that mice that lack KAI1 (also known as CD82), a tetraspanin family member, display higher angiogenic capacity compared to their WT counterpart. Intriguingly, KAI1 was primarily expressed on mural (perivascular) cells in both humans and mice. We next asked if KAI1 expression changes in response to angiogenic stimuli. Angiogenic cytokines reversibly reduced mRNA level of KAI1 in mural cells through Src/PKC-DNMT3A-mediated DNA methylation of *Kai1* promoter region. On the other hand, endothelial KAI1 expression showed no significant changes upon angiokine treatment. Furthermore, protein level of KAI1 also was rapidly lowered upon cytokine stimulation through endocytosis. Our study suggests perivascular KAI1 may act as a switch regulating the transition between vessel quiescence and angiogenesis.

Keywords: Angiogenesis, Vascular endothelial cell, Mural cell, Tetraspanin, KAI1, DNA methylation, Endocytosis

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Introduction

Angiogenesis refers to the process in which a new blood vessel grows from an existing vessel. Since blood flowing through vessels provides nutrient and oxygen and carries away wastes from tissues, the vascular system is of critical importance in the body. Naturally, angiogenesis is a crucial biological process not only affecting developmental process but also adult physiology. Angiogenesis is mediated by a variety of factors including, but not limited to, growth factors such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), angiopoietin, and so on.

Mature blood vessels consist of two cell types: lining endothelial cells and enveloping mural cells. Mural cells in large vessels are called vascular smooth muscle cells and in small vessels pericytes. Mural cells are known to contribute to vessel stabilization and maintain endothelial homeostasis. However, whether and how mural cells directly regulate angiogenesis (i.e. affect ECs so that they cannot respond to angiogenic signals) remain unclear.

The tetraspanin family consists of molecules with four membrane spanning domains. Tetraspanin molecules have been mostly known as ‘molecular facilitators’, which aid other signaling molecules rather than directly participate in molecular pathways. KAI1, also known as CD82, is a member of the tetraspanin family, and has been extensively studied as a tumor metastasis suppressor [2]. However, recent evidence shed light on physiological roles of KAI1 as a functional prospective marker for adult stem

cells including hematopoietic stem cells [3] and myogenic cells [4].

Considering KAI1 suppresses cancer dissemination and angiogenesis is crucial in the process, it is possible that KAI1 blocks tumor angiogenesis. Indeed, there have been a few studies reporting pro- or anti-angiogenic role of KAI1 in tumor environment. [1, 5, 6] However, currently available literature only focused on endothelial cells and tumor cells, leaving mural cells underappreciated. Importantly, we previously discovered anti-angiogenic role of mural KAI1 and identified leukemia inhibitory factor (LIF) as a downstream effector molecule (unpublished data).

Angiogenesis is strictly controlled by achieving balance between pro- and anti-angiogenic regulators [7]. For instance, serum levels of angiostatin and endostatin, major physiological anti-angiogenesis inhibitors, decreased upon surgical removal of primary colon tumor [8]. Therefore, we wondered whether KAI1 expression will change in angiogenic niche. Here, we demonstrate that in angiogenic microenvironment, mimicked by angiogenic cytokine treatment, a signaling cascade consisting of cytokine receptor – Src/Protein Kinase C (PKC) – DNA methyl transferase (DNMT) was activated to downregulate *Kai1* transcription in mouse mural cells. Angiokine stimulation also lowered KAI1 protein level of mouse mural cells by endocytosis.

Results

1. KAI1 is primarily expressed in mural cells

Previous observation revealed that *Kai1*$^{-/-}$ mice demonstrate higher angiogenic capacity [1]. Therefore, we sought to identify which vascular cell type is responsible for the phenotype – in other words, which cell type is a primary source of KAI1.

Blood vessels mainly consist of endothelial cells (ECs) and mural cells (i.e. smooth muscle cells in large vessels and pericytes in capillaries). We analyzed KAI1 expression *in vitro* using a murine endothelial cell line (MS1), mural cell line (10T1/2). RT-PCR, western blot and immunofluorescence images consistently indicated that mural cells express higher level of KAI1 (Fig 1A-1D) than ECs. Notably, the same tendency was observed in human primary endothelial cells (human umbilical vein endothelial cell, HUVEC) and mural cells (human brain vessel pericyte, HBVP) (Fig 1E-1G).

2. KAI1 expression is regulated by angiogenic cytokines both at the genetic and protein level

Considering KAI1 negatively regulates angiogenic activities, we speculated that KAI1 expression would be decreased in an angiogenic niche. When treated with vascular endothelial growth factor (VEGF-A), basic fibroblast growth factor (bFGF) and platelet-derived growth factor (PDGF-bb), 10T1/2 showed a rapid (within 24 hours) decrease in KAI1 expression both at the

genetic and protein levels. Notably, VEGF-A induced a transient reduction in KAI1 expression whereas bFGF and PDGF-bb had a prolonged effect at least up to 72 hours after cytokine treatment (Fig 2A, B).

Interestingly, MS1 show no significant changes in KAI1 level 48 hours after treatment with 50ng/ml or 100ng/ml of each growth factor (Fig 2C-2E). To sum up, our results indicate that mural cells, but not endothelial cells, regulate their KAI1 expression in angiogenic milieu.

3. KAI1 expression is downregulated by angiogenic cytokines, which is mediated by cytokine receptors

In order to determine whether such cytokine-induced changes are mediated by their receptors, we pretreated chemical inhibitors of VEGFR/FGFR/PDGFR and then examined whether it could efficiently prevent cytokine-induced KAI1 downregulation.

Pretreatment of tyrosine kinase inhibitors that block angiokine receptors blocked the downregulation of KAI1 expression, indicating that cytokine-induced KAI1 reduction was mediated by the receptors of each cytokine (Fig 3A-3C). We also confirmed the expression of angiogenic cytokine receptors (VEGFR/FGFR/PDGFR) in murine vascular cells (Fig 3D). Our data reveals that KAI1 expression is reduced in response to angiogenic stimuli, and such response is mediated by receptors for the angiogenic cytokines.

4. Angiogenic cytokines activate PKC/Src, which in turn

increases methylation of *Kai1* promoter region

To further elucidate the downstream effect of the angiogenic cytokines, we pretreated inhibitors that block seven putative signaling molecules (TGF-β, Src, PKC, MAPK, Akt, p53, JAK) one hour before cytokine treatment. Blocking Src and PKC pathways almost completely reversed the effect of all three angiogenic cytokines. (Fig 4A) These data indicate that PKC and Src are downstream of the cytokine receptors.

Next, we investigated how KAI1 expression is suppressed in the presence of angiogenic cytokines. One of the possibilities is that angiogenic stimuli may cause methylation in the promoter region of *Kai1*. Indeed, treatment of cytokine cocktail (combination of VEGF-A, bFGF, PDGF-bb) induced DNMT3A expression, which was inhibited by blocking Src or PKC pathway (Fig 4B).

Bisulfite sequencing revealed that methylation rate of *Kai1* promoter region is elevated when treated with cytokine cocktail, which could be blocked by pretreatment with Src/PKC inhibitor (Fig 4C-4D). Altogether, our data show that angiogenic cytokines activate Src and PKC to increase DNMT expression, finally leading to elevated methylation in *Kai1* promoter region.

5. Angiogenic stimulation induces KAI1 downregulation at the protein level in mouse mural cells

Next, we investigated the mechanism by which KAI1 is lowered at the protein

level. Our group recently showed that KAI1 molecules expressed on the surface of long-term repopulating hematopoietic stem cells are ubiquitinylated and subsequently undergo degradation. Therefore, we hypothesized mural KAI1 would be ubiquitinylated when treated with angiogenic cytokines. Indeed, when given angiogenic stimuli (a combination of VEGF-A, bFGF, PDGF-bb: 100ng/ml each) 10T1/2 cells displayed rapid (within 20 minutes) influx of surface KAI1 molecules.

Discussion

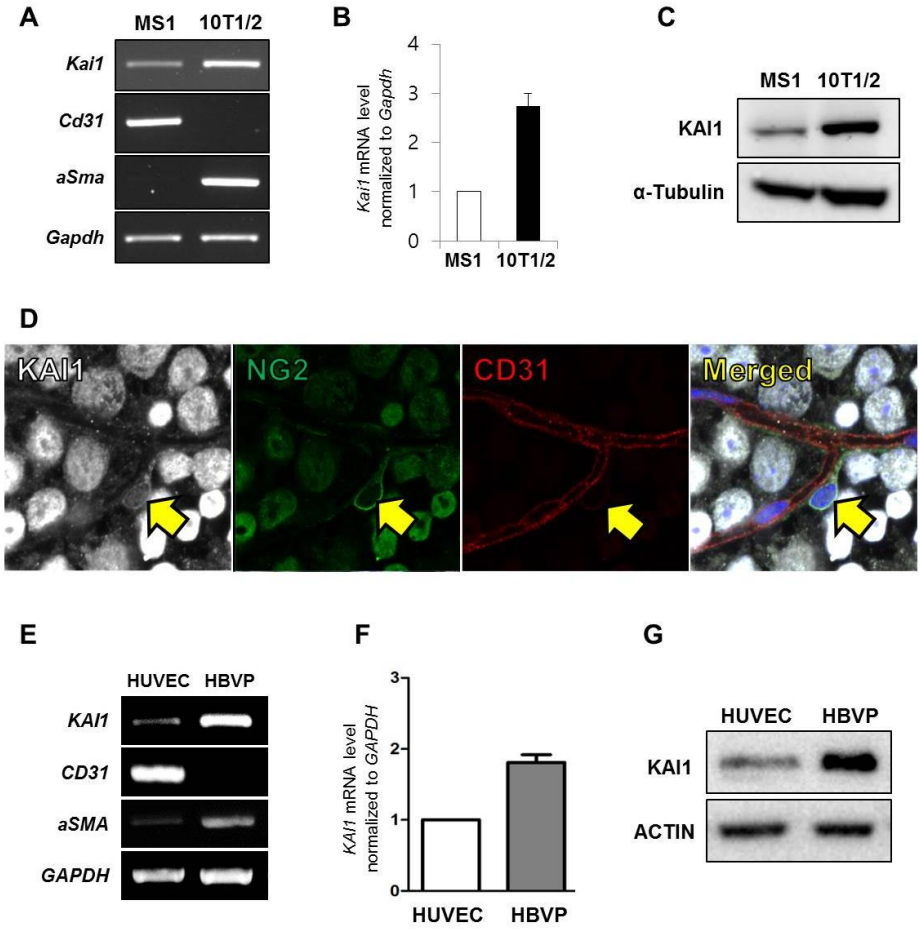
In this study, we showed that KAI1, an antiangiogenic molecule, is mainly expressed by mural cells both in mice and humans. In the presence of angiogenic cytokines, expression of mural KAI1 rapidly decreases both at the genetic and protein level. Importantly, such phenomenon was confined to mural cell population; endothelial KAI1 was unresponsive to the angiogenic cytokine treatment. Our study implies the functional importance of mural cells in regulation of angiogenesis and suggests that KAI1 may be a contributing factor in maintaining the angiogenic balance.

24 hours is a relatively short period of time for DNA methylation or changes at the protein level to occur. Interestingly, mounting evidence indicates DNA methylation of certain genes can occur within as short as 24 hours and methylation status of such genes governs circadian rhythm [9]. However, we cannot exclude the possibility of additional mechanisms other than protein ubiquitinylation. Post-translational modification (e.g. palmitoylation, glycosylation etc.) may account for translocation of KAI1 protein. Indeed, when palmitoylation is inhibited by 2-bromopalmitate, an established palmitoylation inhibitor, membrane localization of KAI1 was decreased (unpublished data). However, to the best of our knowledge, there is no literature addressing the relationship between angiogenesis-stimulating cytokines and palmitoylation in vascular cells. Further study is warranted to explore the possibility that angiokines alter post-translational status of pro- or anti-angiogenic regulators to affect angiogenic capacity.

Endothelial cells are known to express DARC (Duffy antigen receptor for chemokines, also known as CD234), which is a binding partner of KAI1. Direct interaction (contact) between the two molecules (tumor KAI1 and endothelial DARC) contributes to metastasis suppression [10]. We previously reported that in the absence of DARC, KAI1 on the surface of long term-repopulating hematopoietic stem cells is ubiquitinylated, endocytosed and degraded [3]. It would be interesting to examine whether - and if so, when - endothelial DARC expression changes in response to angiogenic stimuli. If we can find a causal relationship between expression level of endothelial DARC and mural KAI1, this will add to the physiological relevance of the KAI1/DARC axis.

Figures

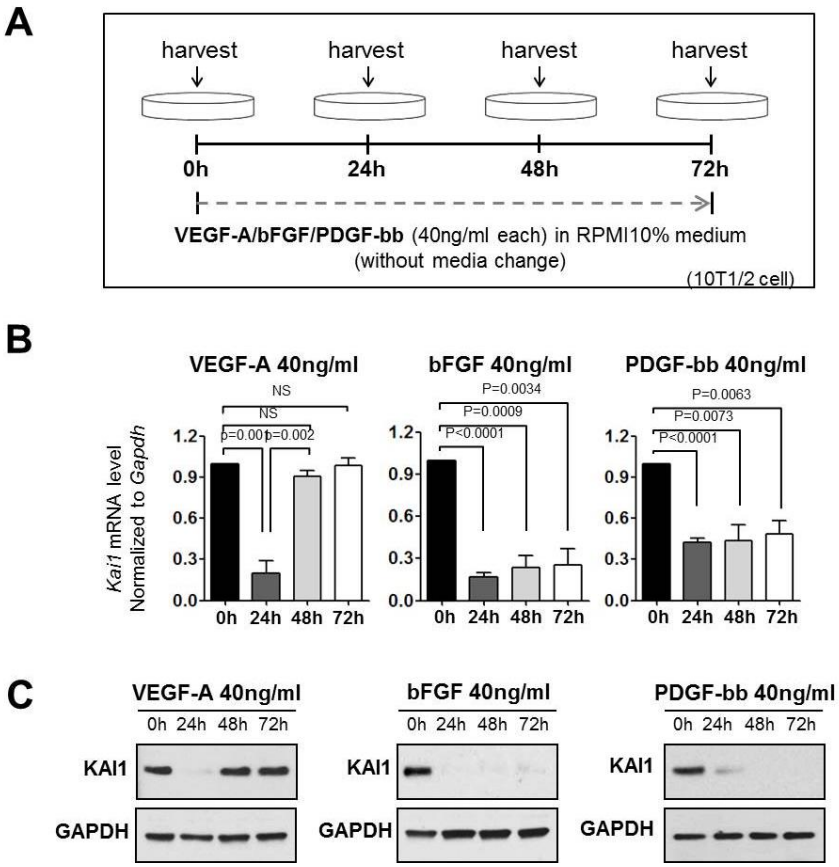
[Figure 1]



(A) mRNA level of *Kai1* in mouse endothelial (MS1) and mural (10T1/2) cell lines. *Cd31* and *aSma* (alpha smooth muscle actin) served as cell type specific markers. *Gapdh* was used as a loading control. **(B)** mRNA expression of *Kai1* in mouse endothelial (MS1) and mural (10T1/2) cell lines measured by quantitative PCR. **(C)** Protein expression of *KAI1* in mouse endothelial (MS1)

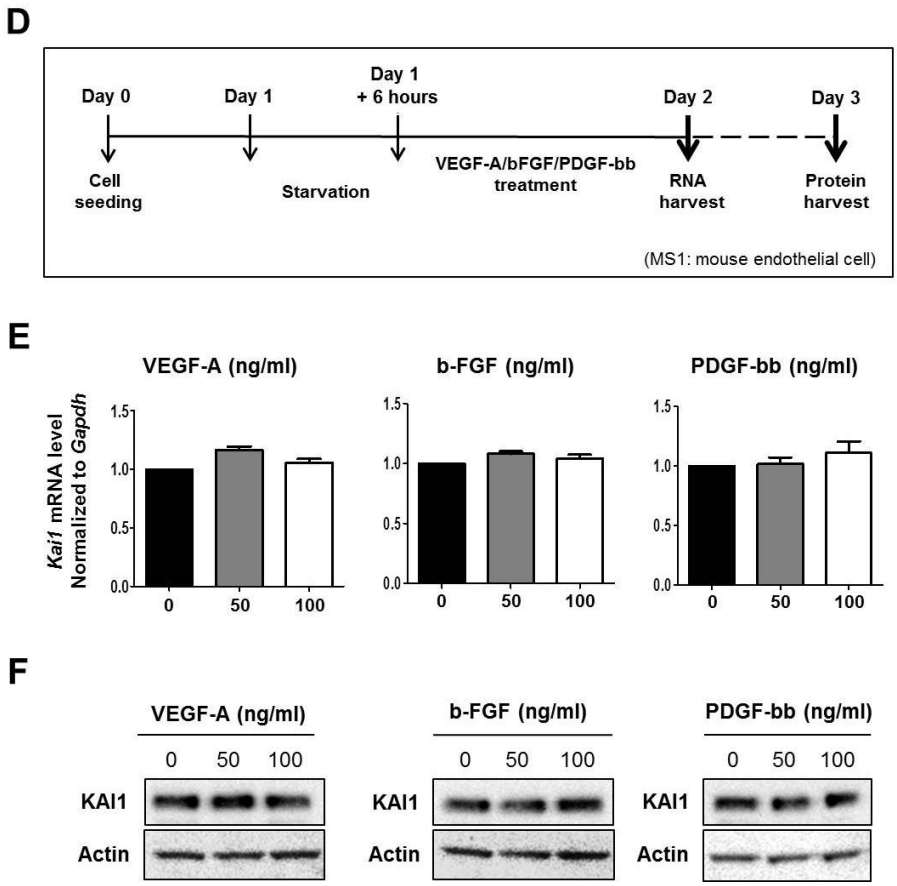
and mural (10T1/2) cell lines. α-Tubulin served as a loading control. **(D)** Immunofluorescence analysis of mouse retinal vasculature (superficial layer) **(E)** mRNA expression of *KAI1* in human primary endothelial (HUVEC) and mural (HBVP) cells measured by RT-PCR. **(F)** mRNA expression of *KAI1* in human primary endothelial (HUVEC) and mural (HBVP) cells measured by quantitative PCR. **(G)** Protein expression of *KAI1* in human endothelial (HUVEC) and mural (HBVP) cell.

[Figure 2]



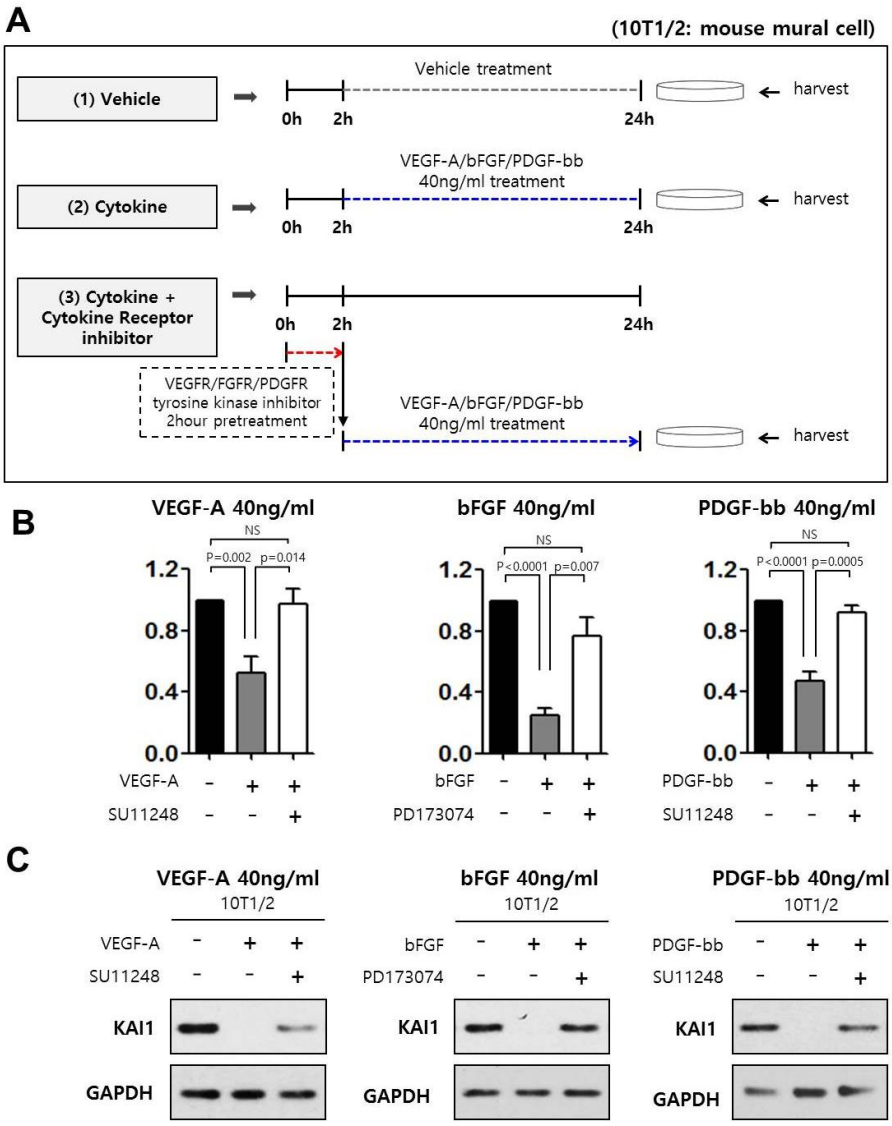
(A) Schematic figure of the experiment **(B)** Time-dependent changes in *Kai1* mRNA level of 10T1/2 after treatment with angiogenic cytokines (VEGF-A, bFGF, PDGF-bb) **(C)** Time-dependent changes in *KAI1* protein level of 10T1/2 after treatment with angiogenic cytokines

[Figure 2, continued]

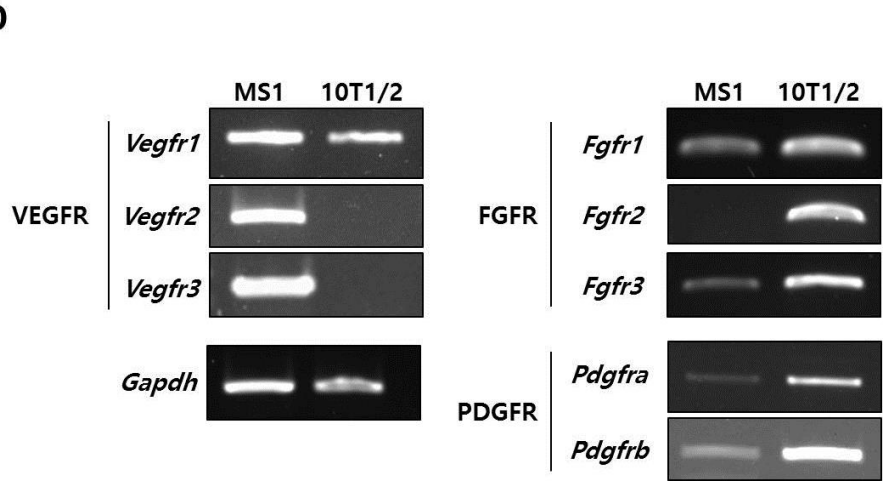


(D) Schematic figure of the experiment **(E)** Dose-dependent changes in *Kai1* mRNA level of MS1 after treatment with angiogenic cytokines **(F)** Dose-dependent changes in *KA1* protein level of MS1 after treatment with angiogenic cytokines

[Figure 3]

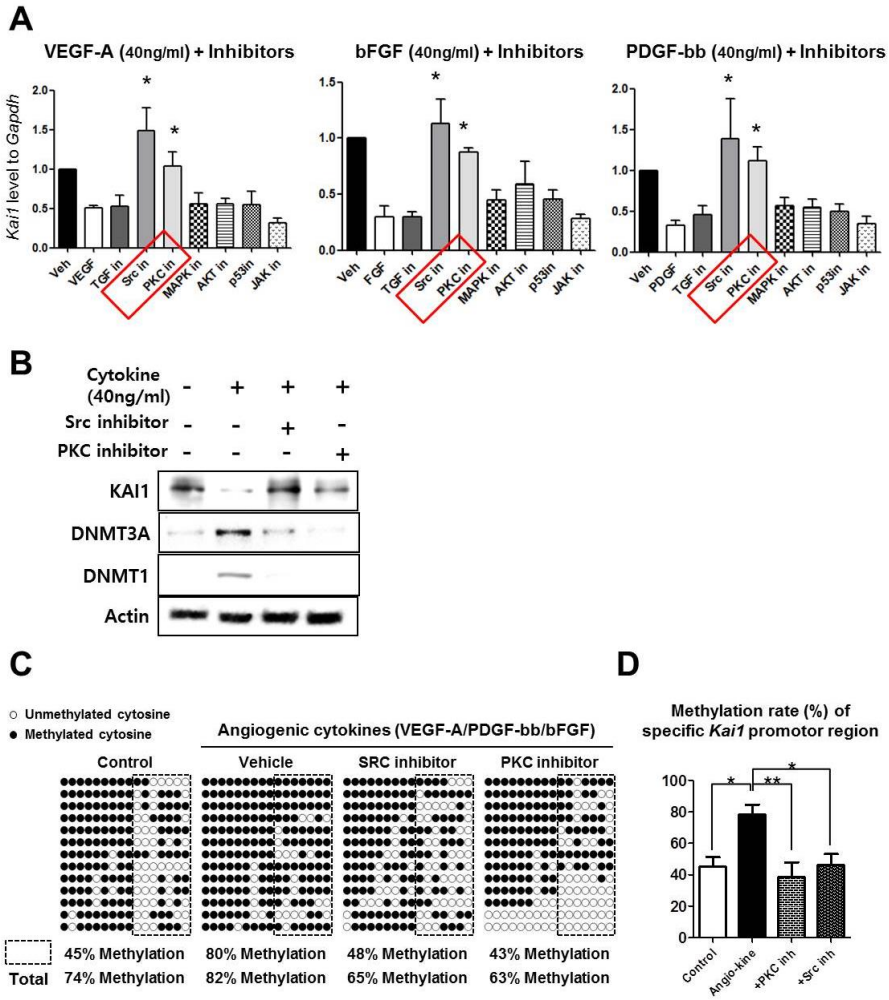

A
(10T1/2: mouse mural cell)
(1) Vehicle
Vehicle treatment
0h
2h
24h
harvest
(2) Cytokine
VEGF-A/bFGF/PDGF-bb
40ng/ml treatment
(3) Cytokine + Cytokine Receptor inhibitor
VEGFR/FGFR/PDGFR tyrosine kinase inhibitor 2hour pretreatment
B
VEGF-A 40ng/ml
bFGF 40ng/ml
PDGF-bb 40ng/ml
NS
P=0.002 p=0.014
P<0.0001 p=0.007
P<0.0001 p=0.0005
VEGF-A
bFGF
PDGF-bb
SU11248
PD173074
C
10T1/2
KAI1
GAPDH

[Figure 3, continued]



(A) Schematic figure of the experiment **(B)** mRNA and **(C)** protein expression of KAI1 in 10T1/2 after (1) vehicle treatment, or (2) cytokine treatment, or (3) tyrosine kinase inhibitor pre-treatment followed by cytokine treatment **(D)** mRNA expression of VEGF receptors (VEGFR), PDGF receptors (PDGFR), FGF receptors (FGFR) in mouse endothelial and mural cell lines

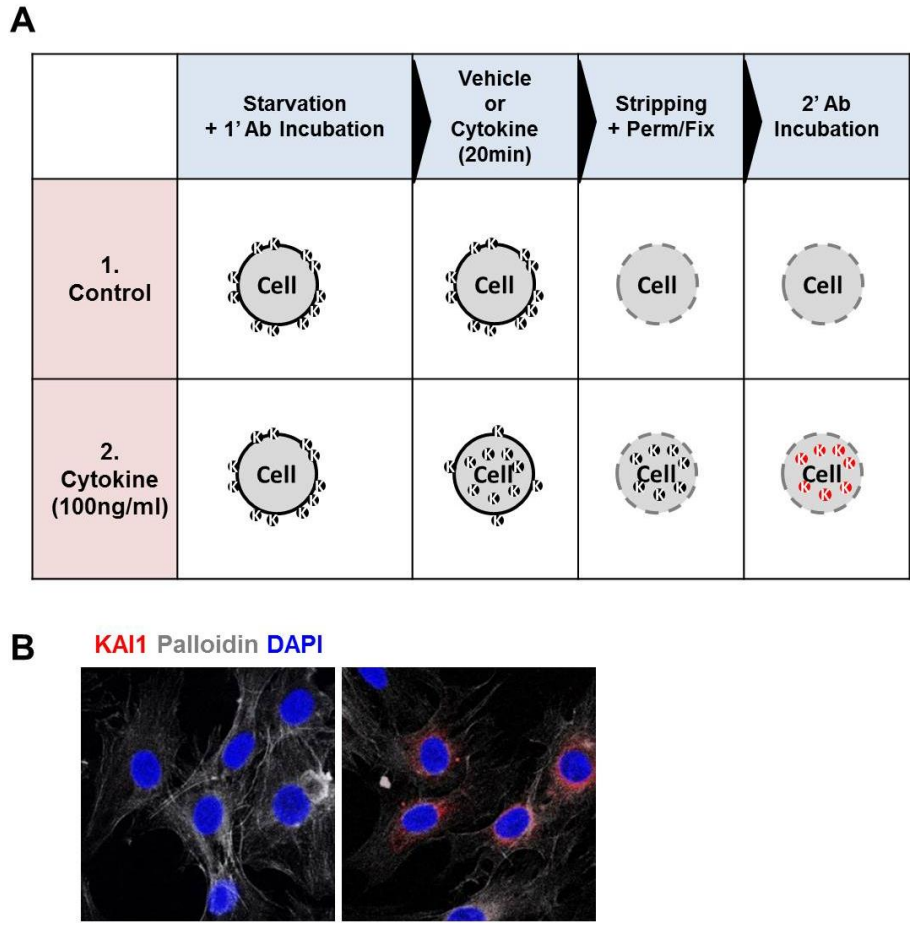
[Figure 4]



(A) *Kai1* mRNA expression (normalized to *Gapdh*) of 10T1/2 after (1) vehicle treatment, or (2) cytokine treatment, or (3) signaling pathway inhibitor pre-treatment followed by cytokine treatment **(B)** Protein expression of KAI1, DNMT3A, DNMT1 in 10T1/2 after (1) vehicle treatment, or (2) cytokine treatment, or pretreatment with (3) Src inhibitor or (4) PKC inhibitor followed

by cytokine treatment. Actin served as a loading control. **(C)** Methylation status of *Kai1* promoter region in 10T1/2 after (1) vehicle treatment, or (2) cytokine treatment, or pretreatment with (3) Src inhibitor or (4) PKC inhibitor followed by cytokine treatment **(D)** Quantification of (C)

[Figure 5]



(A) Schematic representation of the experiment **(B)** Immunofluorescence analysis of subcellular distribution of KAI1 in 10T1/2 cells after angiogenic cytokine treatment. Palloidin marks cytoskeletal structure (therefore morphology) of individual cells.

Materials and Methods

Cells

MS1 (mouse endothelial cell line) was cultured in DMEM high glucose (Gibco) supplemented with 10% FBS (Gibco) and 1X Antibiotics-antimycotics (Gibco). C3H/10T1/2 (mouse pericyte cell line) was maintained in RPMI 1640 HEPES (Gibco) supplemented with 10% FBS (Gibco) and 1X Antibiotics-antimycotics (Gibco). HUVEC (human primary endothelial cell) was cultured in EGM-2MV (Lonza). MS1 and HUVEC were cultured in 1.5% gelatin-coated dishes. Human brain vessel pericyte (HBVP) was purchased from ScienCell and cultured in poly-L-lysine coated dishes using Pericyte Medium (ScienCell).

Gene expression analysis

Total RNA was extracted using TRIzol reagent (Invitrogen) according to the manufacturer's instructions. Reverse transcription PCR was performed as previously described. Briefly, cDNA was synthesized using a Primescript 1st strand cDNA synthesis kit (Takara) and oligo-dT primer. Semi-quantitative PCR was performed with Maxime PCR Pre-Mix (Intron) according to manufacturer's instructions and real-time PCR was performed with Power SyBR Green I Mastermix (Applied Biosystems) using an ABI PRISM TM 7500 Sequence Detection System (Applied Biosystems). Details of primers used in the assay are provided in Supplemental Tables.

Western blot

Cells were lysed with lysis buffer (Cell Signaling) containing protease

inhibitor cocktail (Roche). Total cell lysate was immunoblotted with primary antibodies against KAI1 (Santa Cruz Biotechnology), tSrc, pSrc (Tyr^{416}), pSrc (Tyr^{527}), DNMT3A, DNMT1 (Cell Signaling), followed by incubation in appropriate HRP-conjugated secondary antibodies (Jackson Laboratories). Actin (Santa Cruz Biotechnology) and α-tubulin (Sigma) served as an internal control.

Immunofluorescence analysis of mouse retina

The animal experiment was approved by Institutional Animal Care and Use Committee (IACUC) at Seoul National University. Mouse eyeballs were collected from 6-8 week old, anesthetized C57BL/6 mice and fixed in 2% paraformaldehyde (Wako) for 45 minutes at room temperature. Then retinas were carefully removed from the eyeballs and were blocked with 1% bpvine serum albumin (Amresco) supplemented with 0.25% triton X-100 (Sigma) overnight at 4℃. Over the next several days, retinas were stained with following antibodies: PE conjugated CD31 antibody (BD Biosciences), Alexa Fluor 488 conjugated NG2 antibody (Millipore), KAI1 antibody (Santa Cruz), Alexa Fluor 633 donkey anti-rabbit IgG antibody (Invitrogen), and DAPI (Invitrogen). Finally, the retina was observed under confocal fluorescence microscope (Zeiss).

Analysis of KAI1 expression in response to angiogenic cytokine treatment

Recombinant VEGF-A, bFGF, PDGF-bb proteins were obtained from R&D Systems and Peprotech. Tyrosine kinase inhibitors (SU11248 and PD173074) and signaling inhibitors (Src inhibitor (PP2) and PKC inhibitor (Staurosporin))

were purchased from Sigma.

Bisulfite sequencing

10T1/2 cells were starved in 1% FBS supplemented RPMI1640 medium and treated with angiogenic cytokine mixture (VEGF-A, PDGF-BB and bFGF; 40ng/ul for each cytokine) or vehicle (DPBS). For cytokine treated group, we additionally pre-treated vehicle (DMSO), PKC inhibitor (Staurosporin, Sigma), SRC inhibitor(PP2, Sigma) 1 hour before cytokine treatment. After washing twice with DPBS, gDNA is harvested using G-spin gDNA preparation kit (Intron biotechnology) in accordance with manufaturer protocol. Following that, gDNA went through bisulfite conversion by EpiTect bisulfite kit (Qiagen) according to manufaturer protocol. Brifely, unmethylated CpG (hereafter un-meCpG) is finally converted to TpG whereas methylated CpG (hereafter meCpG) remains as it was. To amplify Kai1 promoter and sequencing the CpG island within it, promoter region was assumed until 3kb before start codon. CpG island was predicted by prediction program for methylation PCR (MethPrimer, China; [11]). Primer set for bisulfite sequencing PCR was manually designed. CpG island within converted gDNA is amplified by bisulfite PCR using those primer set with following condition and then inserted into TA vector via TA cloning kit (Enzynomics). After sequencing it via universial primer (M13F&R), meCpG and un-meCpG is manually confirmed and indicated as Lollypop diagram by comparing the sequencing result with reference sequence; matched (black) or unmatched (white) one, respectively.

Endocytosis assay

Mouse mural cells (10T1/2) were starved in RPMI 1640 supplemented with 0.1% FBS and at the same time treated with primary antibodies against KAI1 (Santa Cruz). Then the cells were treated with angiogenic cytokine cocktail (VEGF-A, PDGF-BB and bFGF; 100ng/ml for each cytokine) or vehicle (DPBS). After 20 minutes post-treatment, cytokines were removed and the surface-bound antibodies were stripped and washed away. The cells were fixed and permeabilized, and underwent secondary antibody (Invitrogen) reaction and were observed under confocal fluorescence microscope (Zeiss).

Statistical analysis

Data are expressed as means ± S.D. The statistical significance of the difference between two groups was evaluated with an unpaired t-test and the significance among three groups was analyzed with one-way analysis of variance (ANOVA) followed by Bonferroni's method. Probability values less than 5% were considered significant. All calculations were performed using SPSS 12.0.

Supplementary Tables

[Table 1] List of primers for detection of mouse genes (RT-PCR)

Gene name	NM accession #	Fwd/ Rev	Sequence (5'→ 3')	Size (base pair)	Tm (℃)
Kai1	NM_007656.5	Fwd	CAGCCACTACAACTGGACAGAG	339	63
		Rev	TACTTGGGGACCTTGCTGTAGT		
Cd31	NM_008816.3	Fwd	GAATGACACCCAAGCGTTTT	328	63
		Rev	GGCTTCCACACTAGGCTCAG		
aSma	NM_007392.3	Fwd	TATGCCTCTGGACGTACAACTG	374	63
		Rev	ATGAAAGATGGCTGGAAGAGAG		
Vegfr1	NM_010228.3	Fwd	CGTGCAAGGAACCTCAGACA	242	60
		Rev	TCAGTCTCTCCCGTGCAAAC		
Vegfr2	NM_010612.2	Fwd	CGGGATAACCTGGCTGACC	361	63
		Rev	CTGTCCCCTGCAAGTAATCTGA		
Vegfr3	NM_008029.3	Fwd	CCCGACTATGTCCGAAAGGG	248	60
		Rev	ATGATGTGGCGTATGGCAGG		
Fgfr1	NM_001079909.2	Fwd	GCCTGAACAAGATGCACTCC	104	60
		Rev	CAGGCCTACGGTTTGGTTTG		
Fgfr2	NM_010207.2	Fwd	CCCTGCGGAGACAGGTAACA	188	60
		Rev	TTTGCCCAGCGTCAGCTTAT		

Fgfr3	NM_001163215.2	Fwd	GCGACAGGTGTCCTTGGAA	244	60
		Rev	CTTGGCAGTACGGTCCTTGT		
Pdgfra	NM_001083316.1	Fwd	GGAACCTCAGAGAGAATCGGC	476	60
		Rev	CCATGTCTGGGTCTGGTACATAG		
Pdgfrb	NM_001146268.1	Fwd	GTTGCCTTACGACTCCACCT	437	60
		Rev	GGTTCAAGTGGCTGGGTAGG		
Gapdh	NM_001289726.1	Fwd	CATTGCTGACAATCTTGAGTGAG	343	59
		Rev	CCCTTCATTGACCTCAACTACAT		

[Table 2] List of primers for detection of mouse genes (Quantitative PCR)

Gene name	NM accession #	Fwd/ Rev	Sequence (5'→ 3')	Size (base pair)	Tm (℃)
Kai1	NM_007656.5	Fwd	GCCCACACCGATGAAGACG	139	60
		Rev	CTTGCTGTTCTTTATCCTGGGTG		
Gapdh	NM_001289726.1	Fwd	GGGATAGGGCCTCTCTTGCT	142	60
		Rev	GTCAAGCTCATTTCCTGGTATGAC		

[Table 3] List of primers for detection of human genes (RT-PCR, Quantitative PCR)

Gene name	NM accession #	Fwd/ Rev	Sequence (5'→ 3')	Size (base pair)	Tm (℃)
KAI1	NM_002231.3	Fwd	CAGGCTCAGGTGAAGTGCT	183	61
		Rev	GTTGCCACTCTGGGTCCT		
GAPDH	NM_002046.5	Fwd	GACAAGCTTCCCGTTCTCAG	185	59
		Rev	GAGTCAACGCATTTGGTCGT		

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요약 (국문초록)

혈관신생 촉진 자극이 주피세포 발현 혈관신생인자인 KAI1/CD82의 발현에 미치는 영향에 관한 연구

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혈관신생과정에서 혈관 벽세포와 테트라스파닌 (tetraspanin) 분자의 다양한 역할이 새롭게 부각되고 있다. 본 연구진을 비롯한 연구자들은 테트라스파닌 분자 중 하나인 KAI1이 결핍되어 있는 생쥐는 야생형 생쥐에 비해 혈관신생이 매우 촉진되어 있는 것을 관찰하였다. 재미있게도 인간과 생쥐 모두에서 KAI1을 주로 발현하는 세포는 혈관내피세포가 아닌 혈관 벽세포였다. 혈관 벽세포에 혈관신생 촉진 인자를 처리해주면 KAI1 발현이 가역적으로 감소하는데, 이는 혈관신생 촉진인자 자극이 Src 혹은 PKC를 경유하여 DNA 메틸화효소 발현을 증가시키고, 이에 따라 *Kai1* 프로모터 부위의 메틸화 정도가 증가하기 때문이다. 혈관신생 촉진인자 자극에 의해 혈관 벽세포의 KAI1 단백질 발현양 역시 세포 내 섭취 (엔도시토시스) 작용에 의해 빠르게 줄어들었다. 한편, 혈관내피세포의 KAI1 발현은 혈관신생 촉진인자 자극에도 변하지 않았는데, 이에 따라 KAI1을 통한 혈관신생의 조절은

혈관벽세포에서 발생하는 일이며, KAI1은 휴면상태 – 혈관형성 상태를 오가게 해주는 ‘스위치’ 역할을 할 가능성이 있다.

주요어: 혈관신생, 혈관 내피세포, 혈관 벽세포, 테트라스파닌, 카이-원, DNA 메틸화, 세포 내 섭취

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