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E EA CH A ICLE

Histone deacetylase controls adult stem cell aging by balancing the expression of polycomb genes and jumonji domain containing 3

Ji-Won Jung · Seunghee Lee · Min-Soo Seo · Sang-Bum Park · Andreas Kurtz · Soo-Kyung Kang · Kyung-Sun Kang

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Abstract A [illegible]. H[illegible] (C) [illegible]. D[illegible] (HDAC) [illegible] (G), [illegible] B I1, E H2 [illegible] 12, [illegible] 3 (J JD3), [illegible] C . [illegible] HDAC [illegible] G [illegible] J JD3. [illegible] G [illegible] HDAC [illegible] B, [illegible] B[illegible] E2F. J JD3 [illegible]. A [illegible] (HA) [illegible] C . [illegible] HDAC [illegible] C [illegible] G [illegible] J JD3 [illegible] 16I K4A [illegible]

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J.- . J[illegible] . L[illegible]

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J.- . J[illegible] · . L[illegible] · .- . [illegible] · .-B. [illegible] · A. K[illegible] ·
K.- . K[illegible] (✉)
A[illegible] C[illegible] C[illegible] S[illegible] K[illegible]
[illegible] @[illegible]

J.- . J[illegible] · . L[illegible] · .- . [illegible] · .-B. [illegible] · K.- . K[illegible]
D[illegible] H[illegible] S[illegible] K[illegible]

. L[illegible] · .- . [illegible] · .-B. [illegible] · A. K[illegible] · .-K. K[illegible] ·
K.- . K[illegible]
BK21 [illegible] S[illegible] K[illegible]

.-K. K[illegible]
D[illegible] B[illegible] C[illegible] S[illegible] K[illegible]

Introduction

[illegible] [1]. [illegible] [2]. [illegible] C 4 [illegible] 2 [illegible] [3, 4]. [illegible] [5] [illegible] H3 [illegible] 4 (H3K4 3), [illegible] C 4, 2 [illegible] A G [illegible] H3K4 3 [illegible] H3 [illegible] 27 (H3K27 3) [illegible].

A [illegible]

Materials and methods

n 10 n⌐ ⚲ 4 ⌐ .C ⌐
n ⌐ ⚲ , ⚲ t⌐ t⌐
⚲ C DL n⚲.

⚲ ⌐ ⌐ ⌐⌐

⚲ ⌐ (A β-⌐) ⌐
n ⌐ [26] ⚲
, . C ⌐ n⌐
1×10^5 / ⌐ n⌐
5×10^4 / ⌐ ⌐n⌐ . C ⌐
3 ⚲ nn-n . E
HDAC ⚲ , ⌐n⌐
2×10^4 / ⌐
1, 3, 5 7 ⌐.C ⚲ ⚲ B
⚲ 0.5% ⌐ ⚲ B (pH 7.2) 5
n . C ⚲ ⚲ C-2-
B (pH 7.2, 1 C-2) ⌐ ⌐
t ⚲ 37°C. C ⚲ ⚲
⚲ B , ⚲ ⌐ H ⚲ 33258
(1 l / ; 10).

I ⚲ ⌐

I ⚲ ⌐ ⌐ HDAC1, HDAC2,
C, B I1, 12, n16[I K4A], E2F-1 B
n . C ⌐ ⚲ 10 A
5 B 5 7 ⌐ 4% n⌐
⌐ ⚲ n ⚲ 0.2% -100
(⌐-A ⚲, L ,). ⚲ ⌐
⚲ 10% (⌐ L I .,
F , CA) ⚲ ⌐ ⚲
HDAC1 (1:200, n B ⚲, L⌐
,), HDAC2 (1:200, n B ⚲),
C (1:100, C , C , CA), B I1 (1:200,
A , C , K), 12 (1:200, A)
n16[I K4A] (1:200, A), E2F-1 (1:200, C)
B (, B , A) ⌐ 1 ⚲
⚲ A 488 A 594 ⌐
(1:1,000; , E ,). ⚲ ⌐
⚲ H ⚲ 33258 (1 l / ; 10). ⚲ ⌐
⌐ n ⚲ n (E n
E200, J n).

⌐

⌐ HDAC1, HDAC2, C,
J JD3, B I1, 12, E H2, n16[I K4A], H3K4 3,
H3K27 3 B n n t
⌐ [25]. C ⚲ HDAC
⚲ 1, 3, 5 7 ⌐ 50
HC ⌐ 0.1% 100 ⚲ ⌐
nn- ⚲ n⌐ /n⚲ n⚲⌐ ⚲ ⌐

(1 n⚲ ⚲ ⌐ , 1 n
1 nn 1 ⌐ n⌐ 0.1
⚲ t⌐). ⌐ n⌐ n⌐ 7.5
15% D - AGE ⚲ ⌐ ⌐
50 , 350 A 5 ⚲. A ⌐
⌐ ⚲ ⌐ , .A
⌐ ⌐ HDAC1
(1:1,000, n B ⚲ ⌐), HDAC2 (1:200, n
B ⚲ ⌐), C (1:100, &D , n-
,), J JD3 (1:500, C), B I1 (1:200,
C⚲ , CA), 12 (1:200, A), E H2
(1:200,), n16[I K4A] (1:200, A), H3K4 3
(1:2,500, A), H3K27 3 (1:2,500, n B ⚲
⌐) B (1:1,000,). S ⌐
⚲ ⌐ ⌐
(A ⚲ ⚲ B ⚲, B ⚲ ⚲ K)
⌐ ⌐ ⚲ n t
⌐ ⌐ ⚲ ⚲ n .

C

⌐ A ⌐
(I t) ⌐ ⚲
. D A ⌐ ⚲ ⚲ n
A ⌐ n A n
(B , K) ⌐ ⌐ ⚲
. C ⌐ ⚲ A C n
(B). ⚲ n ⚲ ⌐
⌐ 1. A C n
n⚲ 1.5% ⌐ ⚲ ⚲
, ⌐ ⚲ ⌐
B G -D ⌐ (B ⌐).
C ⌐ ⌐ C
I J ⌐ (I
H ⚲, L A). E ⚲ ⌐ ⚲
⚲ L13A ⚲ n . A ⌐ ⚲
n n ⌐ ⚲ .

A ⚲ ⌐

E n HDAC1 HDAC2 ⚲ A ⚲
n ⌐ A
HDAC1 HDAC2 ⚲ ⌐
A (D⚲ n A n , ⌐.
L-003493-00, L-003495-00, D-001210-01-05). A
⌐ ⌐
. I ⌐ ⌐
5×10^4 / , A (⚲
⌐) ⌐ ⚲ 50%
. C ⌐ ⚲ 50 100
A 48 96 ⚲. t ⌐ ⚲
HDAC ⚲ 48 ⚲ n
A ⌐

24 ... A... 72 ... A, ... A β- ... ...

C... ... ...

...AD- C... CB- C ... 10- ... ... 0.8×10^5 ... 4 A... 2 B... 7 ... C ... ... 5×10^5 ... 10- ... 7 ... C... I ... ... (C... I ... B...). C... ... ... C ... 1:50, ... C ... 1.5 2% ... ... G - D ... (B... -). ... - C ... - C ... I J ... (... I ... H ... A). E ... ... C... I ... 2.

... ...

A... ($n = 3$), ... ± D. ... (A A), ... D ... ... A t ... $p < 0.05$ ... ...

Results

... CB- ... AD- C ... HDAC, - C ... G

I... ... CB- ... AD- C ... B ... ... C ... (F 1). A ... 19 ... , CB- ... AD- C ... ...

... (A β-) ... (F . 1). ... C ... : ... (... 10 ...), ... (10 15 ...) ... (... 16 ...). I ... CB- ... AD- C ... (... 50% ... C), ... (F . 1). ... ... HDAC1 ... HDAC2, ... HDAC ... , ... C ... HDAC ... ... C ... . I... , A ... ... HDAC1, HDAC2 ... C ... ... C (F . 1 ; F 1A). I... ... ... (F 1C).

... A ... ... G , ... B I1, 12 ... E H2, ... J JD3 ... CB- ... AD- C . A ... , 16 K4A ... C . I... , ... EED ... ... C , ... C ... (F . 1 , F 1B). I... ... 16 K4A ... 27 ... H3 (H3K27), ... C... I ... ... H3K27 ... H3K4 (... ... ... E H2 ... ...) (F . 1). I ... ... H3K27 (H3K27 3), ... , H3K4 3.

I... HDAC , - C ... G ... , ... C . A ... , ... HDAC, - C ... G ... I ... ... , ... A ... F 4, ... HDAC1 ... HDAC2 16- ... (-) B6 ... ... 50% ... 3- ( ) . I... , G ... 20 30% ... , ... C ... ... 10% ... . H ... , ... , ... C ... 60% ... ... - (F 4).

Fig. 1 n- ⎮ t ⮕ ⨎g CB-⎮ ⨎ gAD- C . **a** C ⮕ n- ⎮ t ⮕ S ⨪ n⎮ (⮕ ⨎⎮ 15 n⎮ ⎮) · ⨪t⮕,⎮ t ⎮·⨪ A β-⎮·⎮ ⎮⮕. **b** C ⮕ ⮕ n-⨎⮕⮕ ⎮·⎮⮕ ⨎ ⨎ n⎮ (⮕ ⎮), ⎮⮕ ⮕ ⎮ (⎮), n-⨎⎮ ⮕ ⮕⎮·⎮ ⮕ 50% ⮕ n⎮ ⮕ ⎮·⨪n⎮ ⎮ (⨎⮕ ⨎⮕ t ⨪n⎮⎮) C . E n ⮕ t ⮕ ⨎HDAC1, HDAC2 ⎮ - C⎮ ⮕ ⨎ ⨪ ⮕ n⎮ ⎮ - ⮕ ⮕ ⮕ ⨎ C ⎮ ⨎⮕ ⨪ - C (**c**) ⎮ ⮕ ⮕·⎮⨪ (**d**). ⮕ ⮕ C ⨎⮕ ⎮ n ⮕⮕ ·t ⨎B I1 (C1), S 12 ⎮ E H2 (⮕⨎

C2) ⎮ ⎮ ⮕ ⎮ n ⮕ t ⮕⨎J JD3. n16^{I K4A} n ⮕ t ⎮ ⮕ ⮕ ⎮ , ⎮ ⨎⮕ ⨪ - C (**e**) ⎮ ⮕⮕ ⎮·⨪ (**f**). g C⨎ ⎮ ⮕ ⮕ n n⎮ ⮕ n ⨎⮕ ⎮ ⨎⮕ n ⮕⮕ ⨎n16^{I K4A} n ⮕ ⮕ ⨎⨪ ⮕ ⨎ ⨎ H3K27 . n ⨎⨪ ⮕ ⨎ H3K27, ⮕ ⨎H3K4, ⨪ ⮕ t ⮕ n⎮ (n18) ⨎ CB- C. ⨪ ⮕ ⨎ n16^{I K4A} n ⮕ ⨪ n ⨎ ⎮ ⎮·⨪. G⎮n⨎ n ⮕ ⎮ ⮕ ⨎ - C ⮕ ⨎ ⎮·⎮ ⨎ ⮕ n ⮕ n ⮕ ·*⎮ ** n ⮕ ⎮· ⮕ ⎮ ⨎ t ⮕⨎ $p < 0.05$ ⎮ $p < 0.005$, ⨪ n t ⮕⨪

I⨎ ⮕ ⨎⨎⮕ ⮕ ⎮ ⨪⎮ t ⨪ ⎮ C ⮕ ⮕

I⮕⎮ n t⮕ ⮕, ⨪⮕ t ⨎ ⎮ 3-⎮⨪ ⎮ ⮕⨎ HDAC ⎮⨎ ⮕, ⨎ ⎮ ⮕ ⨪ ⎮ (⎮B) ⎮ ⮕ t⎮⮕ ⎮ (A), ⮕ n21^{CI 1/ AF1} n ⮕⮕ ⎮ C ⮕ ⨎ G2/ n⨎⎮ ⮕⨎⨎ ⮕·⨪ ⨎

⎮⨎⮕ ⮕ n16^{I K4A} n ⮕⮕ ⮕ ⮕ ⮕ ⮕ **27** . I ⨪⎮ ⨎⎮ n n n ⮕⮕⨎ n21^{CI 1/ AF1} ⨪ ⨎ ⨎⮕ ⮕ ⮕⎮ ⮕ ⨎HDAC ⎮⨎ ⮕ (10 ⎮ 5 ⨎ A ⮕ ⎮B, n t ⮕⨪)n⎮ ⮕ ⮕⮕ ⎮ ⮕ ⮕ ⨎ n16^{I K4A} n ⮕ ⮕ ⮕ ⎮ ⮕ ⨎ ⮕⮕ ⮕ . I⮕ ⮕ ⎮ ⨪⨎ ⨎ HDAC ⮕t t ⮕ ⮕·⎮ ⮕ ⮕⮕⨎ C, ⨪ ⮕ ⨎

◀ **Fig. 2** ɡ — —⅛ HDAC ｜ t ⸹ ｜ ｜- n ▪ C
▪ ▪ . **a** HDAC ▪ɡ — , A ｜ ｜B, ▪ ▪ ｜
▪ ▪ ▪ɡ CB-｜ ▪ɡ AD- C ▪ 7 ｜⸹—⅛ ▪ ▪
- , ɡ S ⸹ A β-｜· ｜▪▪.L ｜-｜— —⅛HDAC1,
HDAC2 ▪ - C n— ▪ HDAC ▪ — ｜ C ▪
t ｜- ⸹ ▪ ɡ ⸹. **b, c** ▪ n — t —⅛
n16^{I K4A}, J JD3, - C, B I1 ｜ S 12 ｜ ▪
▪ ｜▪-⸹ .B ɡ ɡ CB-｜▪ɡ S AD- C ｜ ｜ ɡ
2 A▪ 1 ｜B S⅛ ɡ ▪ ｜ n — . ▪-
— ｜ —⅛ɡ ▪ — ⸹ ▪ ▪ , ｜▪ ▪- ｜
▪-⸹ ▪ n⅛ ｜ ▪ ▪ ｜▪ ɡ ."
d — ɡ ▪ — ｜- H3K27 ｜▪ H3K4 ɡ⸹-｜—▪
- t - ｜ ▪ ▪ ▪- ｜▪⸹ ▪ — —⅛
HDAC ▪ɡ — ▪ɡ CB- C . **e** C — ｜ ⅛ 7 ｜⸹,
｜▪ Cɡ I ｜ ｜⸹ S n ⅛ — ｜▪⸹ ɡ — ▪ ɡ⸹-｜▪
n｜ ▪ ɡ n16^{I K4A} n — — ▪ A ⸹ ｜ — ⅛H3K27 3
▪ ɡ ▪,▪ —⅛H3K4 3, ｜— t ▪ ɡ A-｜▪ ｜B -
｜ ɡ S CB- C . F — —▪ n16^{I K4A} n — ｜ ⸹
n ⸹ S n ｜ ｜ ɡ ｜ ｜-⸹

▪ ⸹ ɡ ⸹ (F . 2｜ ; F 2). ɡ — -
t｜—▪ ɡ｜ ▪ɡ — ▪▪⅛ HDAC ｜ t ⸹ ⸹
ɡ ｜- ▪ɡ — , A ▪ ｜B, - ▪ C ·-
-｜ ▪ ▪ ｜▪, ｜— n-｜ t ▪ ▪—⅛
C ,— ▪ ｜-— ▪⅛- C.
I▪▪ — ⅛ ɡ — ▪ ɡ ɡ — -｜ ɡ｜-
▪ —⅛HDAC ▪ɡ — - ｜ ｜- ▪ ▪▪
-｜— ɡ｜—⅛ n-｜ t ▪ ▪ , ▪ — ⅛
— - C (F 3)｜▪ ▪▪ n-
▪ (F . 2 ,)⅛ ɡ ｜⅛ ▪▪ ｜ , ɡ｜
- C, G , J JD3 ｜ n16^{I K4A}. ɡ CB-｜▪ɡ AD-
C ɡ ▪ ｜ n — ▪⅛- C, B I1 ｜▪
12. J JD3 ▪｜ n ｜ ⸹ 1-｜⸹ ｜ ▪—⅛
HDAC ▪ɡ — , ｜▪ n — ▪- t-n｜ ｜ 3 ｜⸹
—⅛ ｜ ▪ n16^{I K4A} ▪｜ - ɡ -⸹ ▪ ｜ ⅛ 3 ｜⸹
—⅛ ｜ ▪ —⅛HDAC ▪ɡ — . I▪ ▪-⸹, ｜ ｜
—⅛B I1 n— ▪ n — ▪▪ ｜ ▪ ▪-⸹⅛▪ ▪ ⸹
- C—▪ ｜-▪ ▪ ɡ｜ B I1 ɡ
｜ ⸹ - C. ▪ ɡ — ɡ ɡ｜▪, ｜- ｜—▪▪⅛
E H2, S 12 ｜▪ J JD3 n — ▪ t- ▪ — t
S ⸹｜⅛ A▪ ｜B ｜ ▪, ▪ ｜ ▪ ɡ｜
ɡ ▪ ｜⸹ɡ｜ t ▪ ｜—⸹ ɡ｜ ▪⅛
ɡ｜—⅛B I1. S n ｜-— ▪⅛n16^{I K4A} n — ▪▪-·-
▪ ｜- ｜—▪ S ▪⅛B I1, E H2, S 12 ▪ J JD3. —
⅛ ɡ — ▪ ▪ɡ ɡ ɡ ｜- ｜—S▪ ⅛E H2｜▪ J JD3
n — ▪- t - ⸹ HDAC ▪ɡ — ｜ ▪ ｜ ɡ -
— ▪-⸹ ▪ ɡ⸹-｜—▪ ▪ n ⅛ ▪- ▪
｜▪ -H3K27 3｜ ▪ ｜▪ -H3K4 3 ｜▪— . A▪ -
▪-⸹, ▪｜— t ɡ｜ ɡ n— ▪ t —⅛H3K27 3,
▪ —⅛H3K4 3, ▪｜ ▪ ▪⸹ ｜▪-⸹ ⸹ ｜ ▪
ɡ 2 A▪ 1 ｜B, ▪ ｜ ▪ ɡ｜ ɡ
｜- ｜— ▪⅛E H2 ｜▪ J JD3 n — ▪- t-｜⅛
ɡ ｜-｜ ▪ ɡ — ▪ ɡ⸹- ｜▪⅛｜ ▪
ɡ⸹-｜ t ⸹, n ｜-⸹▪ ▪-⸹ ▪ 27 — ⅛
ɡ — ▪ H3 (H3K27). S ▪ Cɡ I , ▪ ⅛ ɡ ｜
▪ɡ ɡ ɡ — ｜-｜- ｜— ▪⅛ ɡ⸹-｜— ▪ n｜ ▪▪

｜ ▪ n — n— 7 ｜⸹, ▪ɡ ▪— t ɡ｜
C ｜ ◥ ｜ ▪ ▪ nɡ ▪ ⸹n ｜ — ▪ A β-｜-
｜ ▪▪ (F . 2｜). HDAC1, HDAC2, - C (—ɡ
— ｜- ｜▪ nɡ nɡ ⸹-｜ ⅛), B I1 ｜▪ S 12
ɡ ▪ ｜ ▪— —- ｜-｜▪ ⅛HDAC ▪ɡ —S-
▪ — ｜- ▪ ▪ ⸹⅛ C , ｜ ɡ ▪ ⸹

Fig. 3 HDAC1 ... HDAC2 ... a, b ... HDAC1 ... HDAC2 ... A ... J JD3 ... - C ... - C ... G ... - C ... c ... HDAC1 ... HDAC2 ... C . HDAC1 ... A β- ... t ...

H ... t ... C ...

... G ... J JD3, ... n16$^{I\ K4A}$, ... HDAC ... t ... A ... HDAC1 ... HDAC2 ... . B ... HDAC1 ... HDAC2 ... - C ... CB- ... AD- C ... 50% ... n ... (F . 3 ,). ... G , ... B I1, E H2 ... 12, ... HDAC ... A. ... J JD3 ... n16$^{I\ K4A}$ ... A- ... HDAC . ... G , J JD3 ... n16$^{I\ K4A}$ ... t- ... A- ... HDAC1 ... HDAC2 ... C , ... A β- ... A ... . I ... t ... HDAC1 ... ... - ... A β- ... t ... HDAC1- ... n (F . 3). ... HDAC ... t ... G ... J JD3 ... n ... t- ... n16$^{I\ K4A}$, ... C .

... HDAC ; B ... HDAC ... G

... HDAC ... t ... t ... J JD3 ... n ... n ... C I ... J JD3 ... H3 (A ... -H3) ... H4 (A ... -H4) ... CB- C .

Fig. 4 HDAC ... J JD3 ... H3 ... A ... 12- ... 24- ... HDAC ... CB- C , C I ... H3 ... H4 ... J JD3 ... I ... J JD3 ...

... H3 ... HDAC ... n16$^{I\ K4A.}$ I ... H3K27 3, ... H3K4 3, ... n16$^{I\ K4A}$ ... HDAC ... E H2 ... J JD3 ... H3K27 3 ... (F . 2). ... HDAC ... G ... J JD3 ... t- ... n16$^{I\ K4A}$ ... C ... H3K27 3 ... n ... .

Fig. 5 HDAC ... C, E H2 ... 12 ... B ... ... **a** HDAC ... ... B ... ... 24 ... ... **b, c** A ... 12 24 ... ... HDAC ... ... CB- C, C I ... ... B ... HDAC1 ... E H2 (**b**) ... 12 (**c**) ... ... I ... ... E2F ...

Fig. 6 A g   (AA),
n t   C   n t   . **a** C   t n -
                  t   .   g   t   g AA-
           n   g g g g   n. **b** A
n t   n   t
                      n   . **c** A   C DL

n   -   - n   g
     t (F   6B).   t,
10058-F4   A β- - t ,   g
    - C t   nt   -   C
(F   6C). A   B I1   n
              10058-F4   CB-
g AD- C   n   g   (F   6D),
              g   - C t   n   g
                     B I1 n   C   .
I , - C t
  n -   C.

H   g   n t   C
      n- t   G
              J JD3   n   t -

g   g HDAC
    t , t   -   G, n   -
          t   n t   C . I
g   , HDAC   t   -
          g n   g J JD3 n   . I
        g n   n   B g
       E H2   12,   B I1
      g - C S   -
      (HA)   HDAC,
g   g   g HA,
    (AA),   n- t   C .
        g AA   g

        t   g CB- C,   t,
g n-   -   g AD- C,   g
          t   n -   t (F . 6,   ). I
                  g   g
C   g
        t   g HA   g   ,   n   g
n   t   HDAC, - C,   G   n 16^{INK4A}
    AA-   C g   n-   g
                t .
            t   n t   g n   t   -
            HDAC2, B I1   12   g
g CB-   g AD- C. A   , HDAC1, - C
  E H2 n   t   n   g CB-
  C   g 10 l AA   n   g
    n (F . 6). H   t, n   -
g AD- C   g AA   t,
n   n
                            ,   g C DL   t
(F . 6).   g n   t   J JD3
                            AA   g g CB-
g AD- C. L   n 16^{INK4A} n   t -
                        AA   g CB- C,
  g AD- C,   n   n   .
                         g   g HA   t
              t   n t   -
    t   g HDAC   g g HA   g   ,   -
        ,   g   g
C .

Discussion

Fig. 7

HDAC

HDAC

Acknowledgment

Open Access

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