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研究課題名(和文) 単一転写因子の発現量の違いによる単球と樹状細胞の分化制御

研究課題名(英文) Molecular mechanisms underlying monocyte and dendritic cell differentiation

研究代表者

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交付決定額(研究期間全体)：(直接経費) 3,100,000円

研究成果の概要(和文)：単球及び樹状細胞(DC)は免疫応答や組織恒常性維持に必須の骨髄由来細胞である。本課題では単球・DC分化過程における細胞種特異的遺伝子発現パターンの形成機構について、転写因子IRF8によるエンハンサー制御の観点から解析を行った。その結果、IRF8は前駆細胞段階において単球やDCに特徴的なエンハンサーに結合し、エンハンサー活性化とその後の遺伝子発現誘導に必須であること、DCの造血早期における運命決定はIRF8がDC系譜遺伝子のエンハンサーのエピゲノムの変化を生じさせることで誘導されることなどがわかった。本研究を進展させることで単球やDCに関わる疾患の新たな治療法開発に繋がることが期待される。

研究成果の学術的意義や社会的意義

本研究により単球・DCの分化過程における転写因子による遺伝子発現制御の詳細を明らかにすることができた。取得した網羅的解析データは全て公共データベースや私たち独自のデータベースであるMyeloid Chromatin Atlas (<http://immunol.med.yokohama-cu.ac.jp/chromatinatlas/>)において利用することができる。本研究で得られた知見やデータにより単球やDCが関与するがんなどの疾患の深い病態理解に貢献できると考えられる。

研究成果の概要(英文)：Monocytes and dendritic cells (DCs), critical for immune responses and tissue homeostasis, are derived from bone marrow hematopoietic stem cells. In this study, we analyzed molecular mechanisms underlying the establishment of cell type-specific gene expression profiles during monocyte and DC development. We found that monocyte- and DC-specific enhancers were gradually established by transcription factor IRF8 at mononuclear phagocyte progenitor stages before the expression of associated genes. We also found that early DC lineage specification is epigenetically controlled by IRF8. These results deepen our understanding of how transcription factors regulate hematopoietic cell differentiation.

研究分野：免疫学

キーワード：血球細胞分化 樹状細胞 単球 転写因子

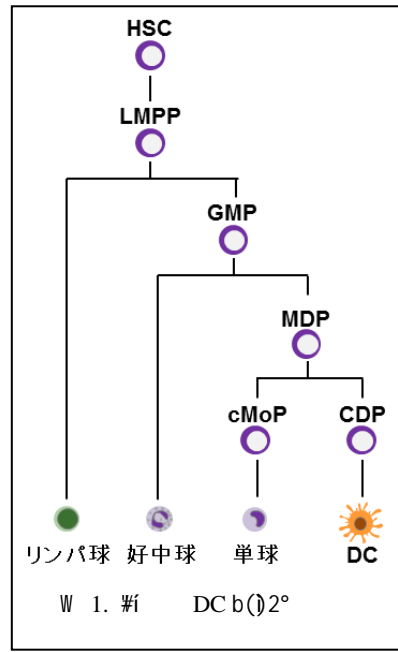
hematopoietic stem cell, HSC
 multipotent progenitor, LMPP
 granulocyte-monocyte progenitor, GMP
 monocyte-DC progenitor, MDP
 common monocyte progenitor, cMoP
 common DC progenitor, CDP

DC S9Q
 MDP
 cMoP
 CDP

DC I b

Naik et al. *Nature* 496, 229, 2013

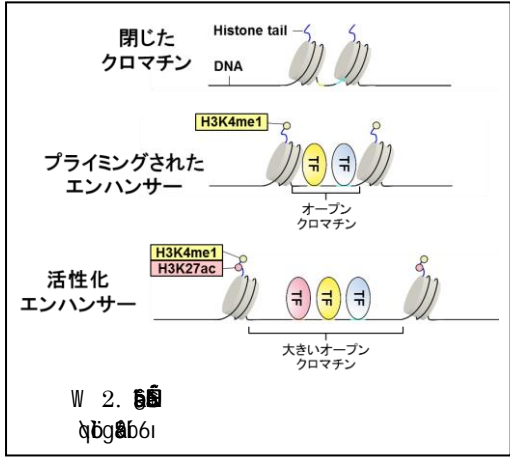
DC 4 b



closed chromatin (閉じたクロマチン)
 primed enhancer (プライミングされたエンハンサー)
 active enhancer (活性化エンハンサー)

H3K4me1
 H3K27ac

W 2. 6

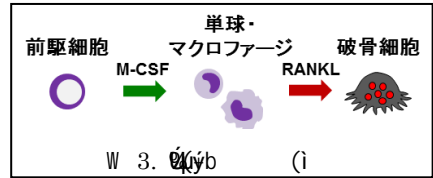


interferon regulatory factor-8 (IRF8)
 Kurotaki et al. *Blood* 121, 1839, 2013; *Nat Commun* 5, 4978, 2014;
Blood 125, 358, 2015; IRF8 Ly6C+ DC b
 1839, 2013; cDC1 pDC IRF8 4G MDP b7u Q
 Hambleton } *N Engl J Med* 365, 127, 2011; IRF8 MDP b7u Q
 K CDP [c] cMoP [c] MDP } c IRF8 p
 cDC1 x pDC c IRF8 IC CDP cMGX IRF8 8rS IRF8
 MDP cMoP IRF8 CDP cMGX IRF8 c MDP } CDP
 IRF8 cMoP } IRF8 8rS IRF8 c MDP } CDP
 IRF8 @ *Klf4* 4GbVegBMG *Klf4* b
 K IRF8 (MGX) IRF8 8rS IRF8 c MDP } CDP
 8 Kurotaki et al. *Blood* 121, 1839, 2013 IRF8 } DC g
 b(DMB) 6

- DC b (4E5)
- DC 4 b (b9pS9Q) b \ DC 4 b DE IRF8 bzm b0'
- IRF8 p 3Rbzm b 0'

C57BL/6
 \ H3K27ac b
 10⁷
 FLKSVKS
 K ChIP-seq
 j b
 LMPP
 RNA-seq / WS
 Assay for Transposase-Accessible Chromatin Sequencing ATAC-seq
 M8GMS2
 4G8
 1213, 2013
 99
 M-CSF
 Z
 H3K27ac x3
 PU.1 b ChIP-seq / WS

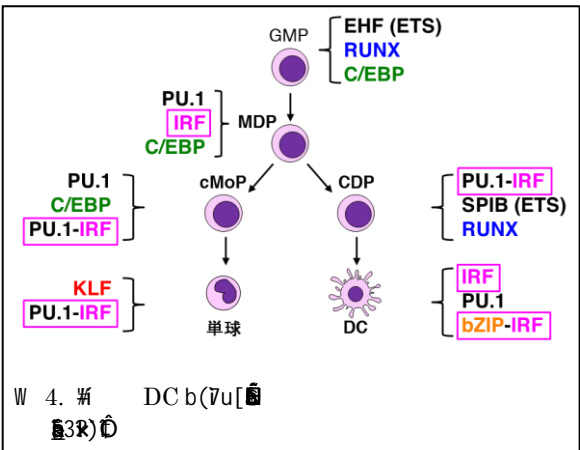
GMP MDP cMoP CDP# DC# 7
 ChIP-seq WSM+
 c 10⁵
 reference genome & mm10
 Bowtie Homer R
 heterogeneity #OMSu
 LMPP
 ATAC-seq
 Buenrostro et al. *Nat Methods* 10,



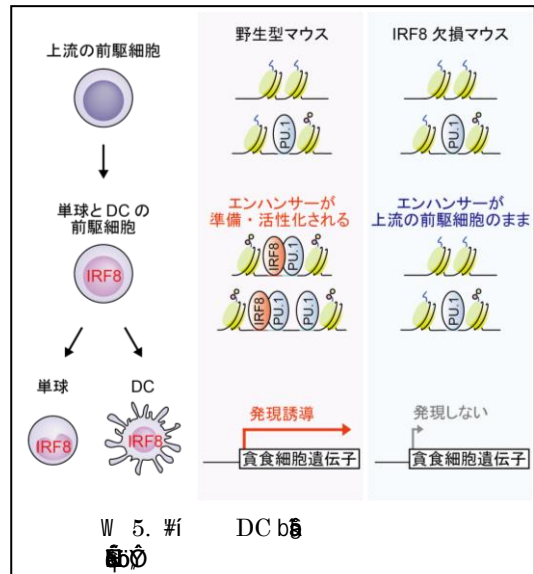
2>2B

(1) #i DC (b)

DC b (4)
 H3K4me1 \ H3K27ac b
 ChIP-seq / WS
 DC
 DC
 DC b (7u)
 MDP ZF
 IRF b
 9 X6
 IRF8 @ MDP
 IRF8
 IRF8
 IRF8
 IRF8
 MDP x cMoP
 MDP x cMoP
 IRF8
 IRF8 @ GMP
 IRF8 @ GMP
 MDP x cMoP



W 4. # DC b (7u)

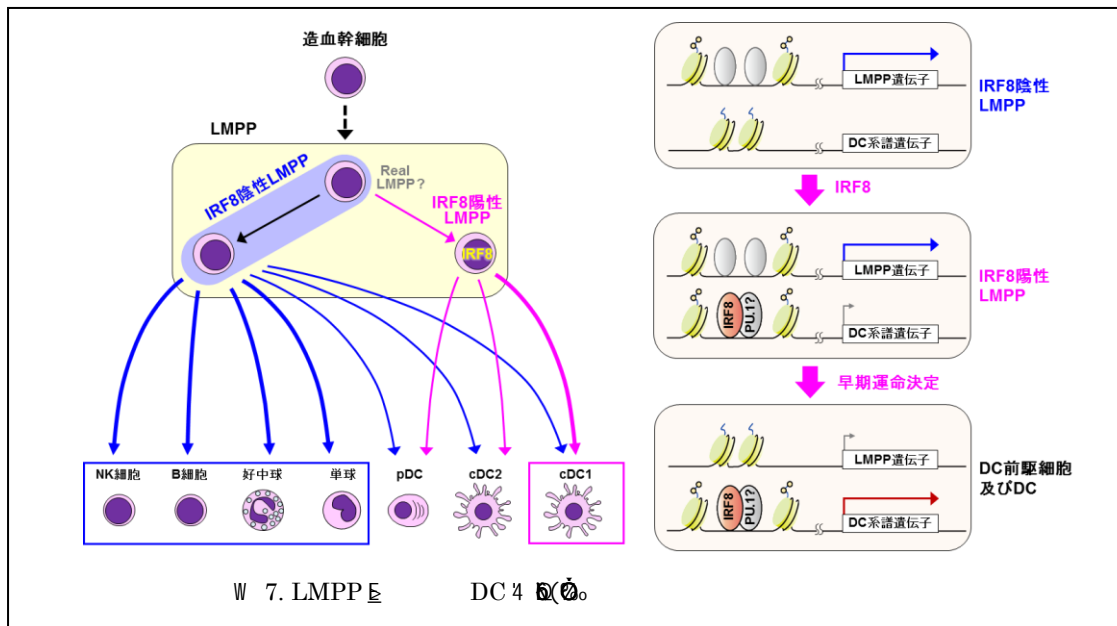
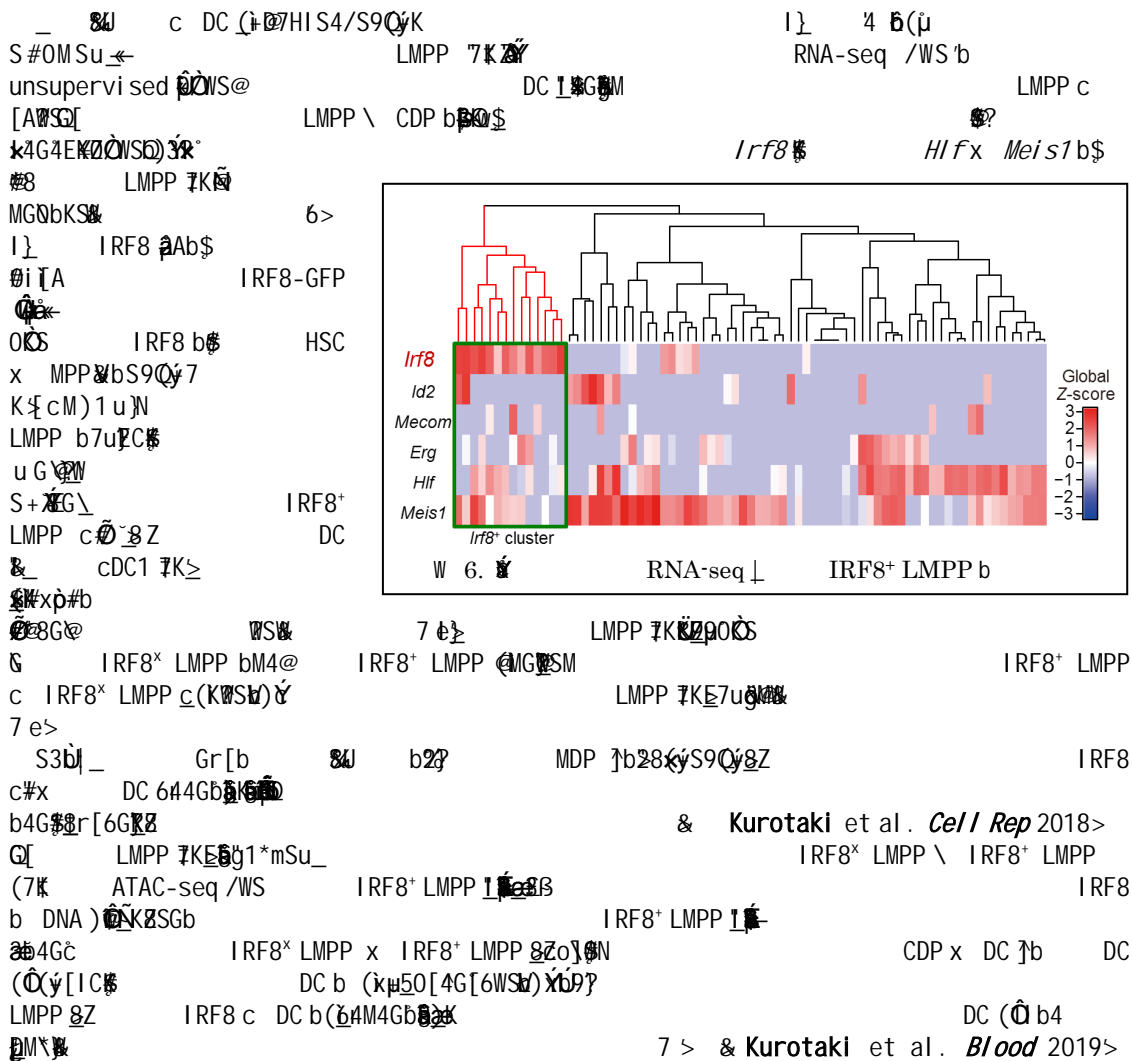


W 5. # DC b

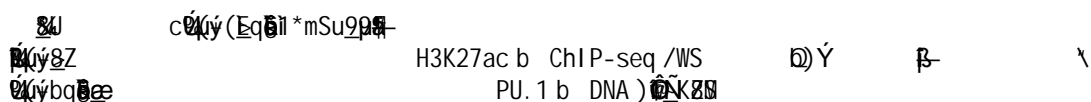
& Kurotaki et al. *Nat Commun*

& Kurotaki et al. *Cell Rep* 2018

(2) DC 4 b0'



(3) DC 4 b0'



Affinity Group Meeting, 2018.

s Nishiyama A, Ban T, Fushimi K, Nakabayashi J, **Kurotaki D**, Tamura T: Stepwise and mutual activation of enhancers and promoters during cell differentiation. *Cell* 174: 103-116, 2018.

t **Kurotaki D**, Fushimi K, OYE I, Nishiyama A, Nakabayashi J, Ban T, Tamura T, Morse HC III, Ozato K, Suzuki Y: IRF8 governs enhancer dynamics during mononuclear phagocyte development. *Cell* 174: 117-130, 2018.

u **Kurotaki D**, pO N,] +B, OYE I, Morse HC III, Tamura T: IRF8 governs enhancer dynamics during mononuclear phagocyte development. *Cell* 174: 117-130, 2018.

v OYE I, Morse HC III, Ozato K, Ban T, pO N, **Kurotaki D**, 134, Morse HC III, Tamura T: IRF8 governs enhancer dynamics during mononuclear phagocyte development. *Cell* 174: 117-130, 2018.

w Sasaki H, Nishiyama A, **Kurotaki D**, Tamura T: A novel distal enhancer responsible for *Irf8* expression in the mononuclear phagocyte lineage. *Cell* 174: 131-144, 2018.

x OYE I, Morse HC III, Ozato K, Ban T, pO N, **Kurotaki D**, Morse HC III, Tamura T: IRF8 governs enhancer dynamics during mononuclear phagocyte development. *Cell* 174: 117-130, 2018.

y **Kurotaki D**: /#(S)QyE(O)D. 2017.

z **Kurotaki D**: IPA qMS/#(y)DM3Rb2. Ingenuity. 2017.

{] +B **Kurotaki D** spO OYE I, Herbert C. Morse III & Keiko Ozato & Se (S) IRF8 c4/82(y)O b(i) DM 1 G7E --wD, 2017.

|] +B **Kurotaki D** spO Herbert C. Morse III & Keiko Ozato & Se (S) qvb(y)S9Qyb 28 G 50r, 2017.

} **Kurotaki D**, Nakabayashi J, Nishiyama A, Sasaki H, Kaneko N, Kawase W, Ozato K, Suzuki Y, Tamura T: Transcription factor IRF8 governs enhancer landscape dynamics during mononuclear phagocyte development. The Annual Meeting of the American Association of Immunologists, 2017.

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Kurotaki D spO Herbert C. Morse III & Keiko Ozato & Se (S) M(y) RNA-seq (y)S9Qyb 21 G4/pX% 2, 2017.

Kurotaki D, Kawase W, Nakabayashi J, Morse HC III, Ozato K, Tamura T: Single-cell RNA-seq reveals a novel dendritic cell-primed early progenitor population. *Cell* 174: 131-144, 2016.

Kurotaki D, pO N, Herbert C. Morse III, Keiko Ozato, Se (S), Morse HC III: M(y) + RNA-seq (y)S9Qyb 78 G7U, 2016.

Kurotaki D: 3R IRF8 (y) bD 22 G/8, 2016.

WE 1 6

q **Kurotaki D**, Morse HC III: /#(y)S9Qyb Sub(y) v 90E 80-90, 2017.

W

D.

q <https://www.yokohama-cu.ac.jp/amedrc/news/201902kurotaki.html>

r <https://www.yokohama-cu.ac.jp/amedrc/news/20180307kurotaki.html>

s <http://immunol.med.yokohama-cu.ac.jp/chromatinatlas/>

t MD <http://www-user.yokohama-cu.ac.jp/~immunol/>