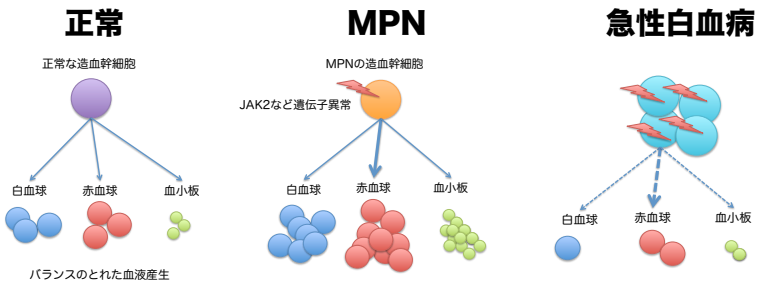
ストレス応答機構とMPN

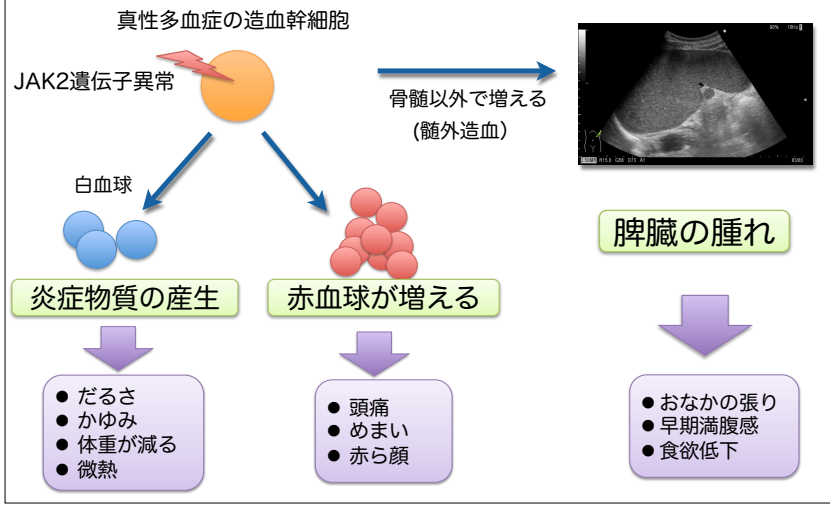
山梨大学　桐戸敬太

骨髄増殖性腫瘍(MPN)とは

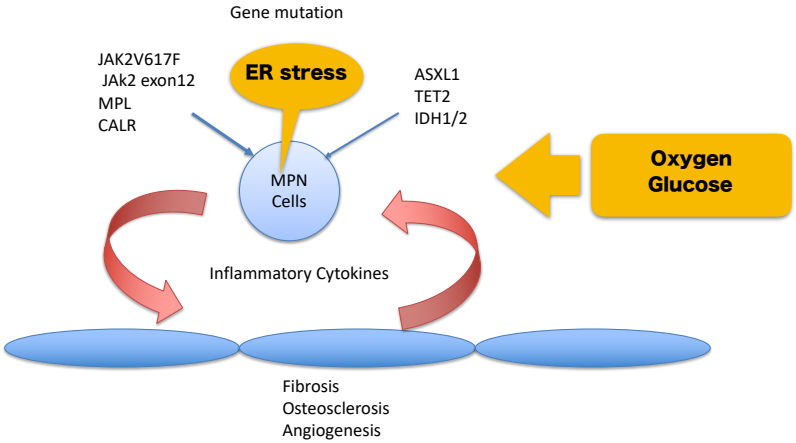
造血幹細胞に生じた異常により、
1 系統以上の骨髄系の細胞が過剰な増殖を示す病態



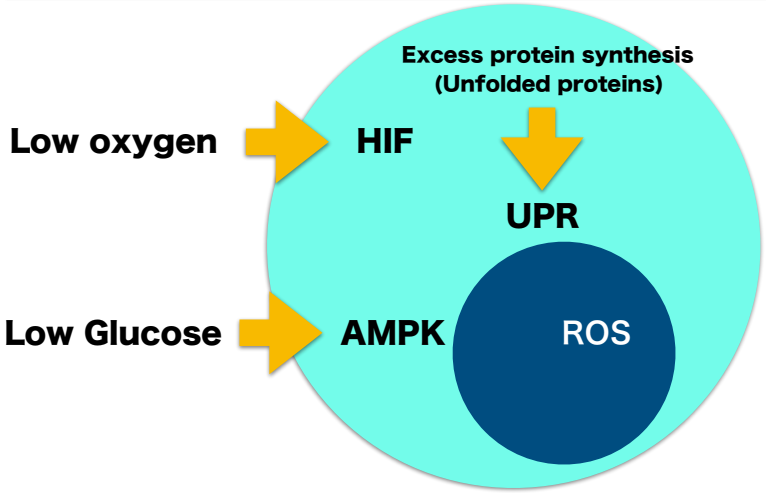
MPNの病態生理と症状



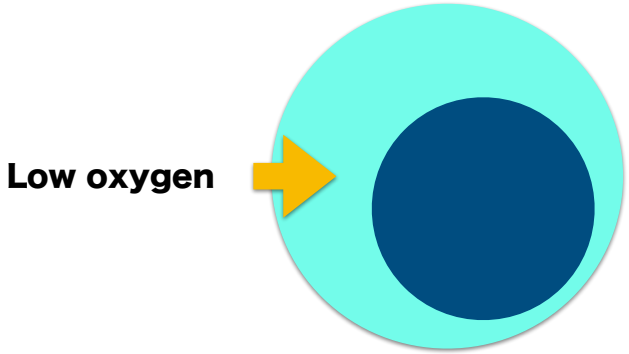
ストレス応答とMPN

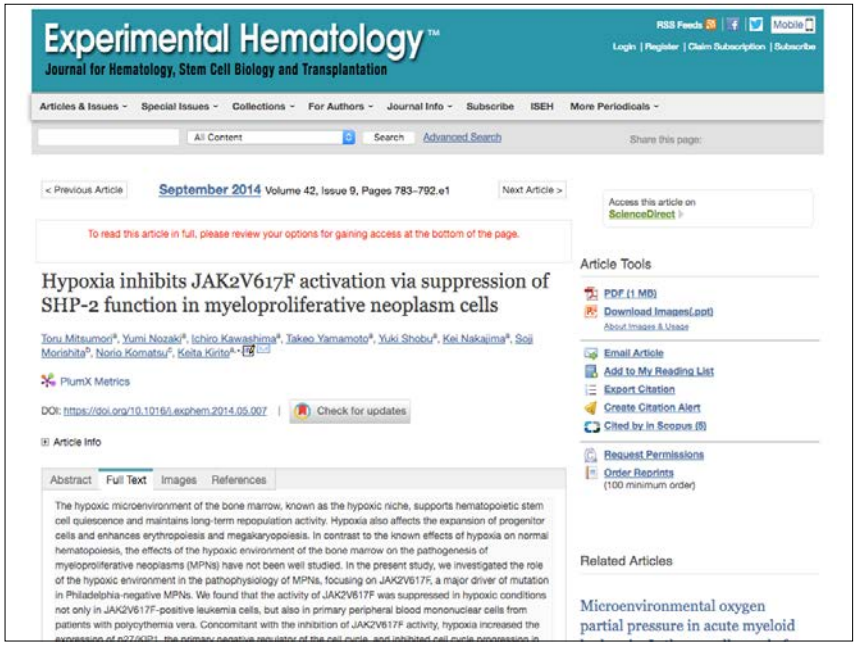


ストレス応答経路



1. 低酸素環境とMPN

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Hypoxia inhibits JAK2V617F activation via suppression of SHP-2 function in myeloproliferative neoplasm cells

Toru Mitsumori[a], Yumi Nozaki[a], Ichiro Kawashima[a], Takeo Yamamoto[a], Yuki Shobu[a], Kei Nakajima[a], Soji Morishita[b], Norio Komatsu[c], Keita Kirito[a,*]

PlumX Metrics

DOI: https://doi.org/10.1016/j.exphem.2014.05.007 | Check for updates

Article Info

Abstract · Full Text · Images · References

The hypoxic microenvironment of the bone marrow, known as the hypoxic niche, supports hematopoietic stem cell quiescence and maintains long-term repopulation activity. Hypoxia also affects the expansion of progenitor cells and enhances erythropoiesis and megakaryopoiesis. In contrast to the known effects of hypoxia on normal hematopoiesis, the effects of the hypoxic environment of the bone marrow on the pathogenesis of myeloproliferative neoplasms (MPNs) have not been well studied. In the present study, we investigated the role of the hypoxic environment in the pathophysiology of MPNs, focusing on JAK2V617F, a major driver of mutation in Philadelphia-negative MPNs. We found that the activity of JAK2V617F was suppressed in hypoxic conditions not only in JAK2V617F-positive leukemia cells, but also in primary peripheral blood mononuclear cells from patients with polycythemia vera. Concomitant with the inhibition of JAK2V617F activity, hypoxia increased the

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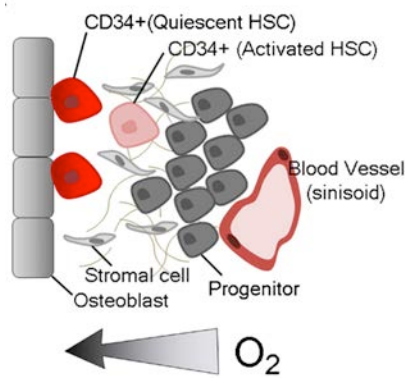
骨髄内は低酸素環境である



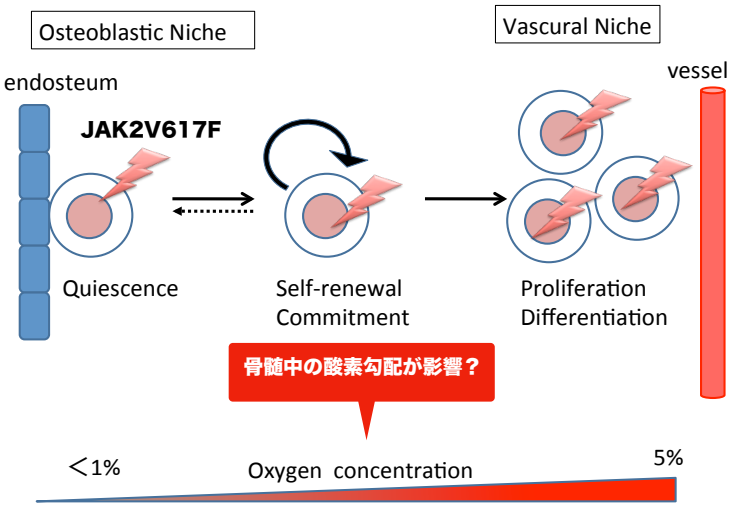
The Hematopoietic Stem Cell Niche

1-6% O_2

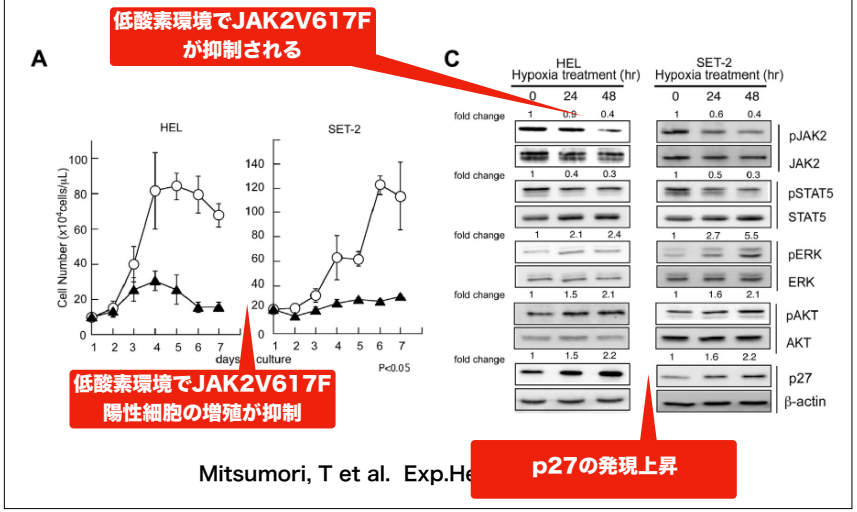
Grant and Root, 1947
Cipolleschi et. al., 1993
Chow et al., 2010
Eliasson and Jonsson, 2010

Mohyeldin M et al. Cell Stem Cell 2010

JAK2V617Fの作用が異なるメカニズム？

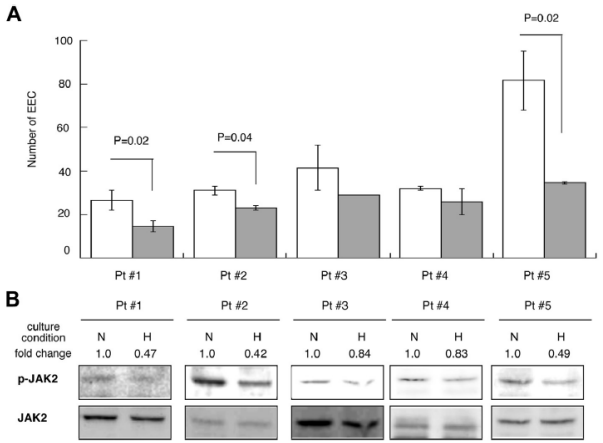


低酸素環境はJAK2V617F活性を抑制する



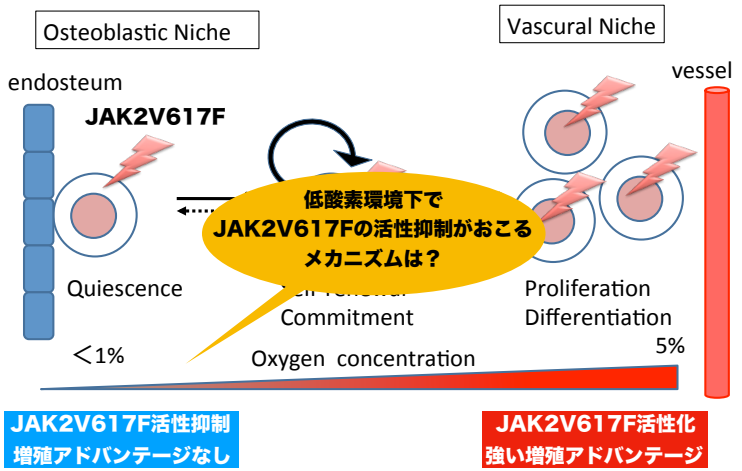
Mitsumori, T et al. Exp.He

低酸素環境はEECを抑制する

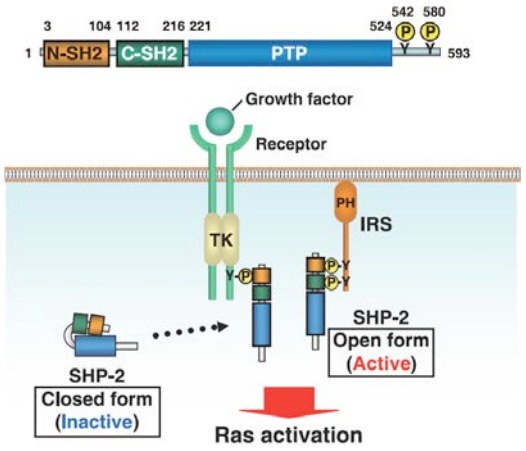


Mitsumori, T et al. Exp.Hematol 2014, 42, 783

JAK2V617Fの機能は造血幹細胞と前駆細胞で異なる



SHP-2の構造と機能



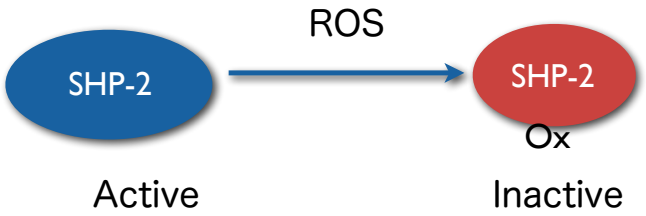
Matozaki T et al. Cancer Science 2009:100;1786

ROSによるSHP-2の機能制御

Molecular Cell, Vol. 9, 387–399, February, 2002, Copyright ©2002 by Cell Press

Reversible Oxidation and Inactivation of Protein Tyrosine Phosphatases In Vivo

Meng, T-C et al.



SHP-2とMPN

www.impactjournals.com/oncotarget/ Oncotarget, 2018, Vol. 9, (No. 5), pp: 6055-6061

Research Paper

Rapid development of myeloproliferative neoplasm in mice with *Ptpn11*^{D61Y} mutation and haploinsufficient for *Dnmt3a*

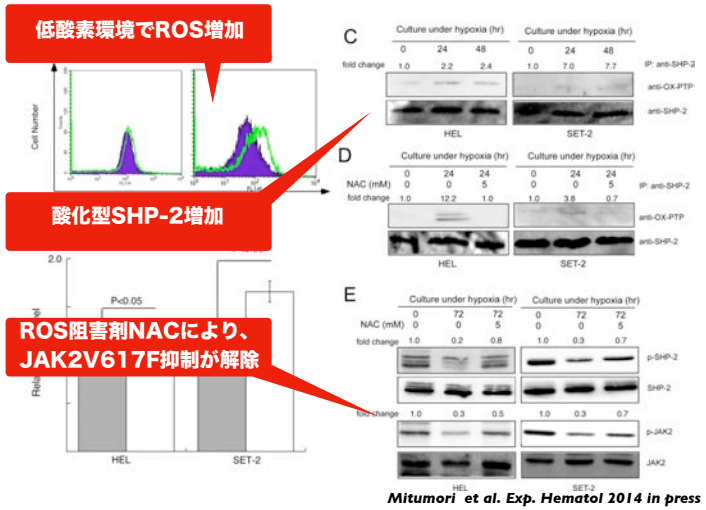
Lisa Deng[1,2], Briana M. Richine[1,2], Elizabeth L. Virts[1,4], Victoria N. Jideonwo-Auman[1,4], Rebecca J. Chan[1,2,4,5] and Reuben Kapur[1,2,3,4]

Published in final edited form as:
Leukemia. 2018 January ; 32(1): 203–213. doi:10.1038/leu.2017.250.

SHP2 Is Required for BCR-ABL1-Induced Hematologic Neoplasia

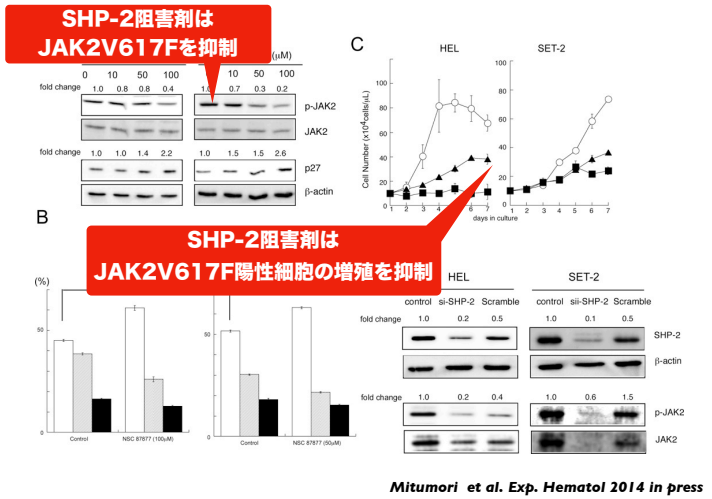
Shengqing Gu[1,2,5], Azin Sayad[2], Gordon Chan[2], Wentian Yang[3], Zhibin Lu[2], Carl Virtanen[2], Richard A. Van Etten[4], and Benjamin G. Neel[1,2,6]

低酸素環境で増加したROSがSHP-2の機能を抑制する



Mitumori et al. Exp. Hematol 2014 in press

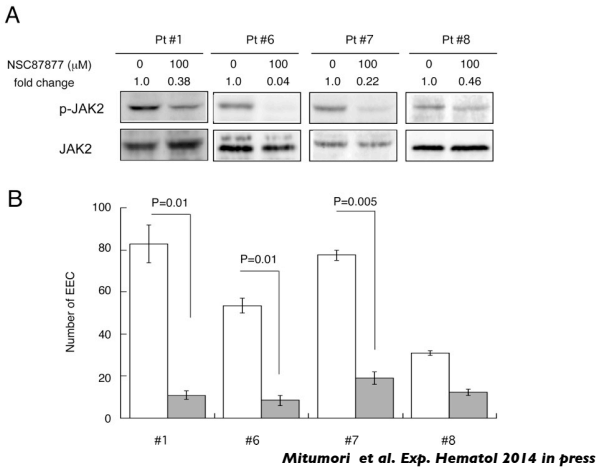
SHP-2の機能抑制は JAK2V617F陽性細胞の増殖を阻害する



Mitumori et al. Exp. Hematol 2014 in press

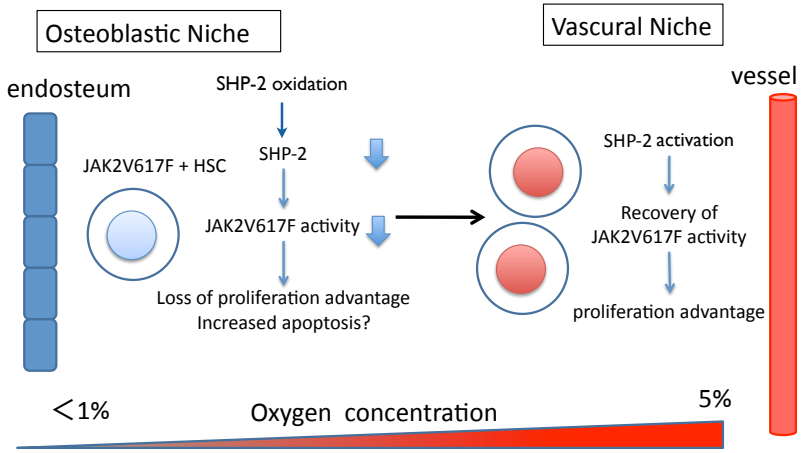
SHP-2阻害剤はPV症例由来の JAK2V617F陽性細胞の増殖を阻害する

Fig.5 Mitsumori et al.

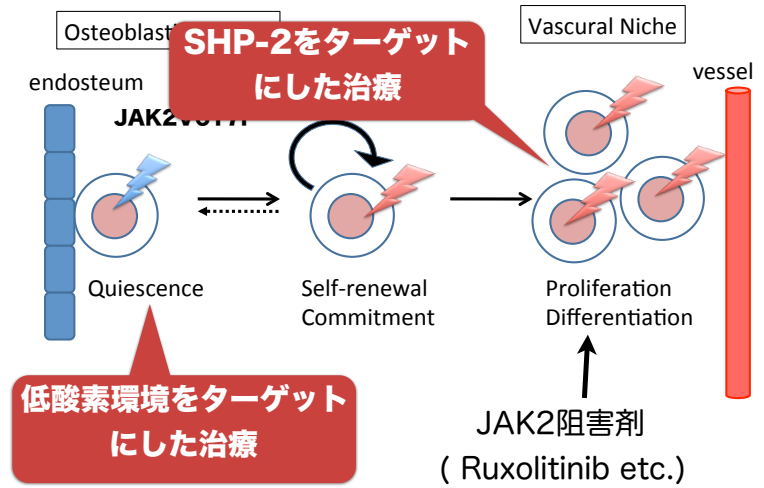


Mitumori et al. Exp. Hematol 2014 in press

サマリー

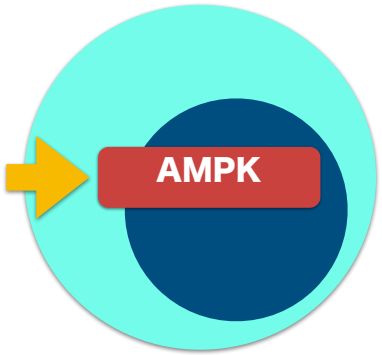


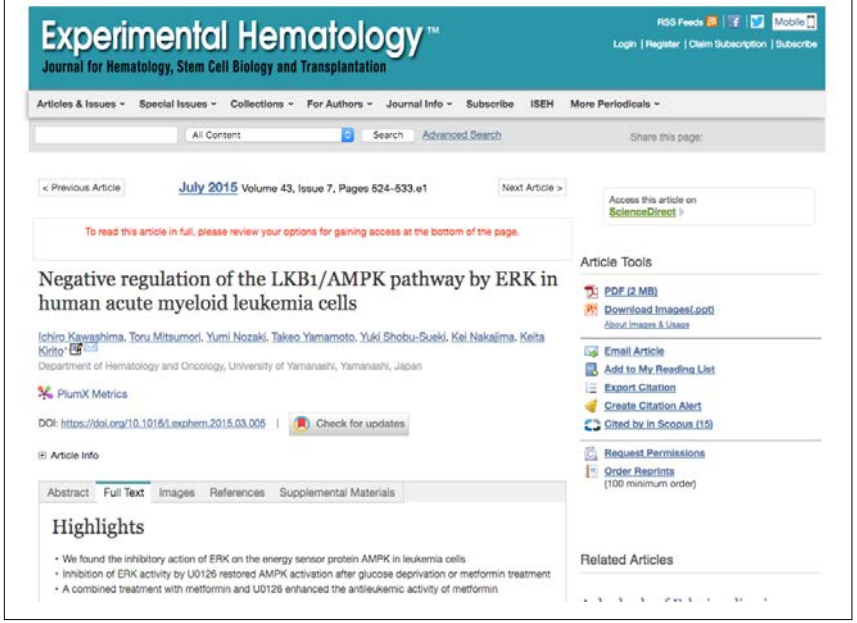
MPNに対する新たな治療戦略



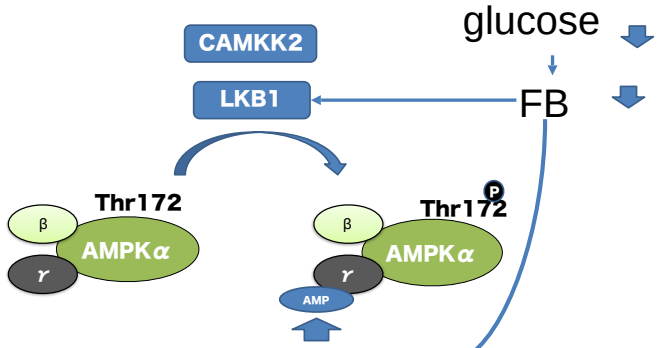
2.グルコース応答系とMPN

Low glucose

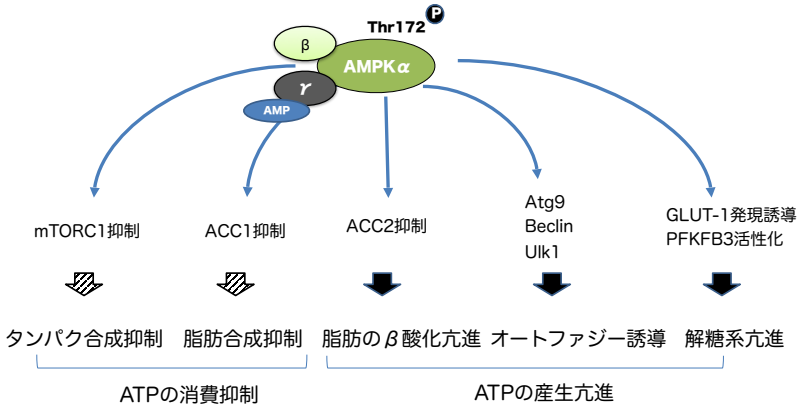




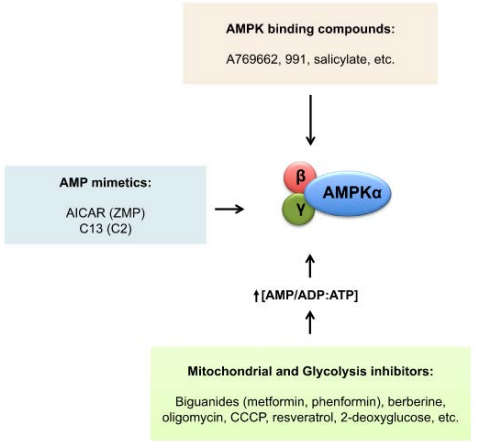
エネルギーセンサー：AMPK



AMPKの機能



AMPK活性化化合物



Metformin

Garcia D and Shaw RJ Mol Cell 2017 66, 789

AMPKと血液腫瘍

MYELOID NEOPLASIA

The LKB1/AMPK signaling pathway has tumor suppressor activity in acute myeloid leukemia through the repression of mTOR-dependent oncogenic mRNA translation

Alexa S. Green,[1-3] *Nicolas Chapuis,[1,2,4] *Thiago Trovati Maciel,[5] Lise Willems,[1,2,6] Mireille Lambert,[1,2] Christophe Arnoult,[3] Olivier Boyer,[3] Valerie Bardet,[1,2,4] Sophie Park,[1,2,6,7] Marc Foretz,[1,2] Benoit Viollet,[1,2] Norbert Ifrah,[7,8] François Dreyfus,[1,2,6,7] Olivier Hermine,[9] Ivan Cruz Moura,[6] Catherine Lacombe,[1-3] Patrick Mayeux,[1,2] †Didier Bouscary,[1,2,6,7] and †Jerome Tamburini[1,2,6,7]

Blood 2010

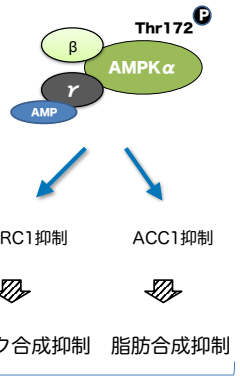
Brief report

Antileukemic effects of AMPK activators on BCR-ABL–expressing cells

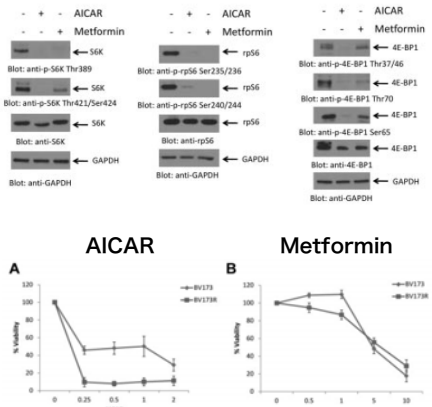
Eliza Vakana,[1] Jessica K. Altman,[1] Heather Glaser,[1] Nicholas J. Donato,[2] and Leonidas C. Platanias[1]

Blood 2011

AMPK活性化によるCML細胞の増殖抑制

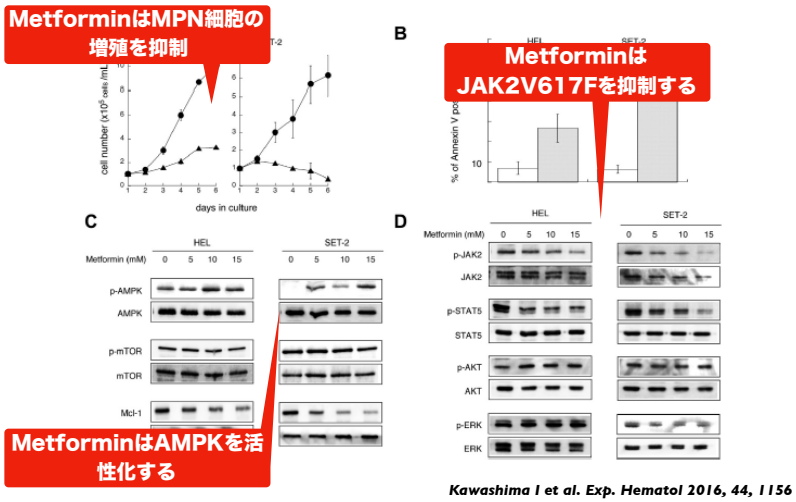


CML細胞の増殖抑制



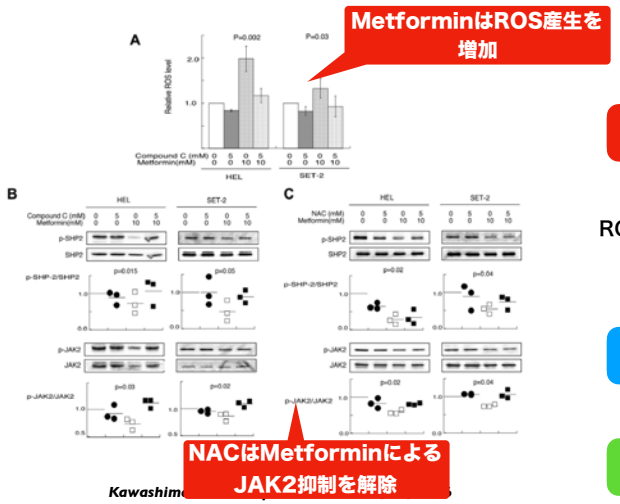
Vakana, E et al. Blood 2011, 118, 6399

MPN細胞に対するMetforminの作用



Kawashima I et al. Exp. Hematol 2016, 44, 1156

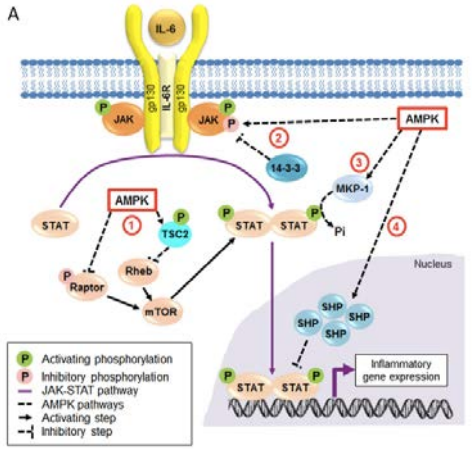
MetforminによるJAK2抑制機序



Metformin
AMPK
ROS production
SHP-2
JAK2

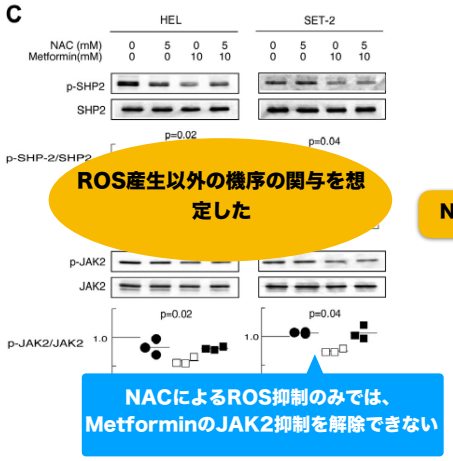
Kawashima

AMPKを介するJAK/STAT抑制



C. Speirs et al. / Pharmacological Research 128 (2018) 88–100

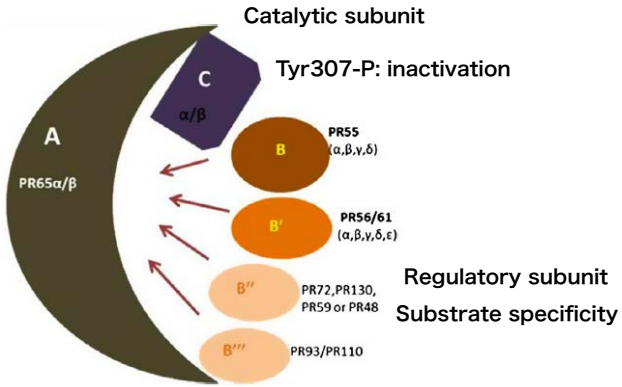
MetforminによるJAK2抑制機序



Metformin
AMPK
NAC
ROS production
SHP-2
JAK2

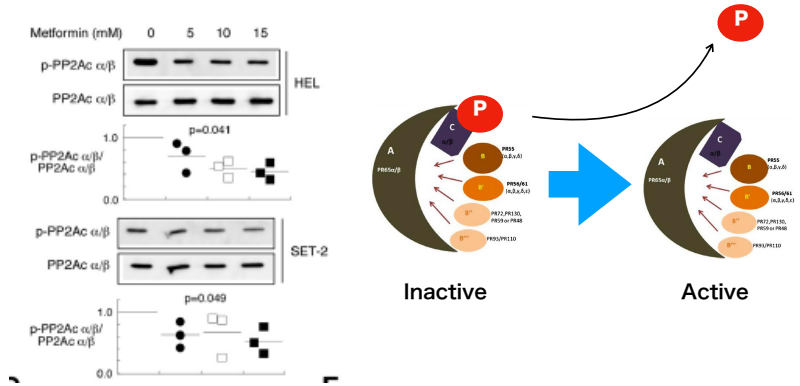
Kawashima I et al. Exp. Hematol 2016, 44, 1156

PP2Aの構造



Seshacharyulu, P et al. Cancer Letters 2013, 335, 9

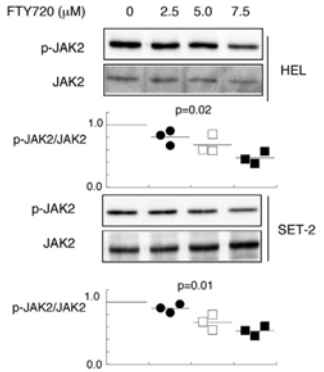
MetforminはPP2Aを活性化する

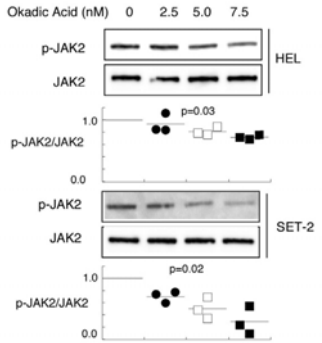


PP2A活性化とJAK2V617F制御

FTY720: PP2A activator

Okadaic Acid : PP2A inhibitor

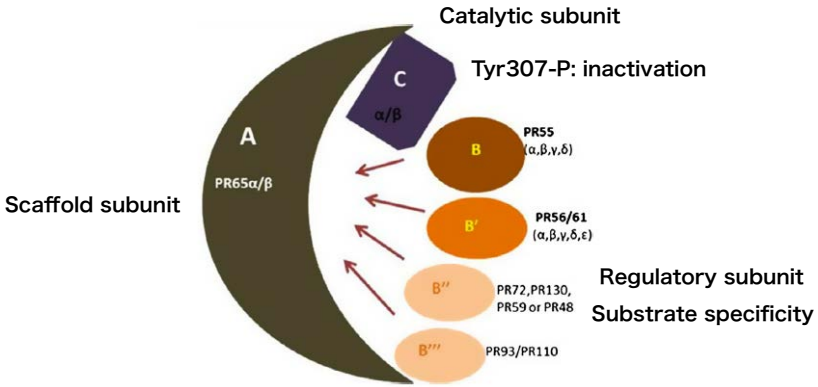




Kawashima I et al. Exp. Hematol 2016, 44, 1156

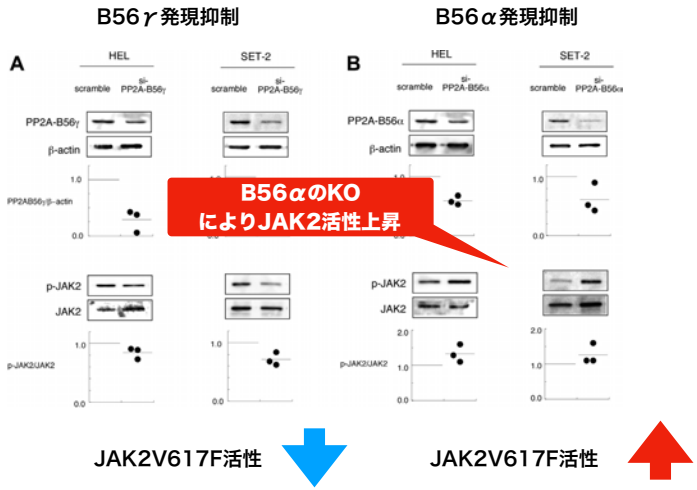
PP2A activatorとPP2A inhibitorともにJAK2V617Fを抑制!!

Bサブニニットに注目



Seshacharyulu, P et al. Cancer Letters 2013, 335, 9

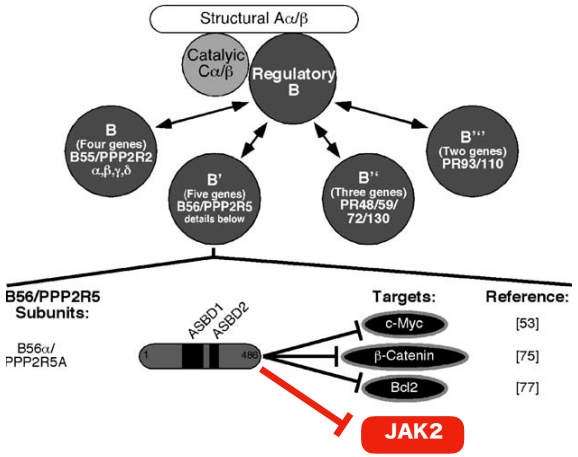
B56αがJAK2V617F抑制に関与



JAK2V617F活性

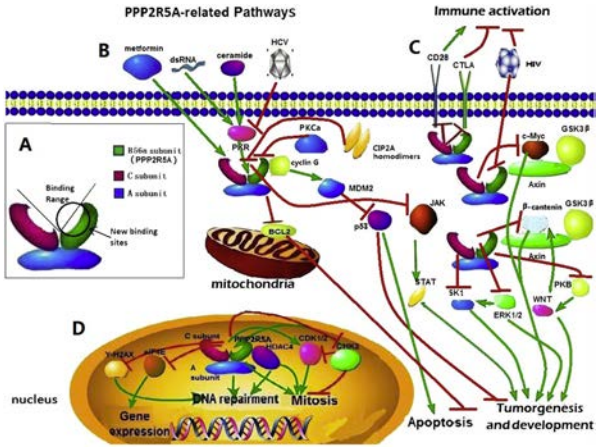
JAK2V617F活性

B56α−PP2Aの機能



Arnold HK and Sears RC Cancer Metastasis Rev 2008, 27, 147

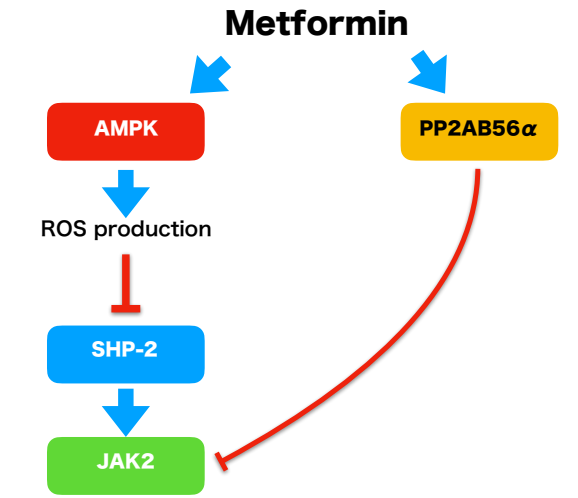
B56α−PP2Aの機能



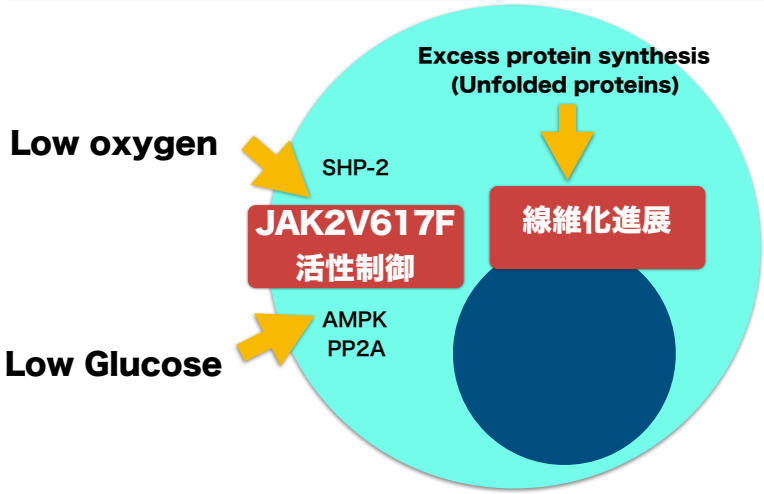
Z. Mao et al. / Cancer Letters 414 (2018) 222e229

サマリー

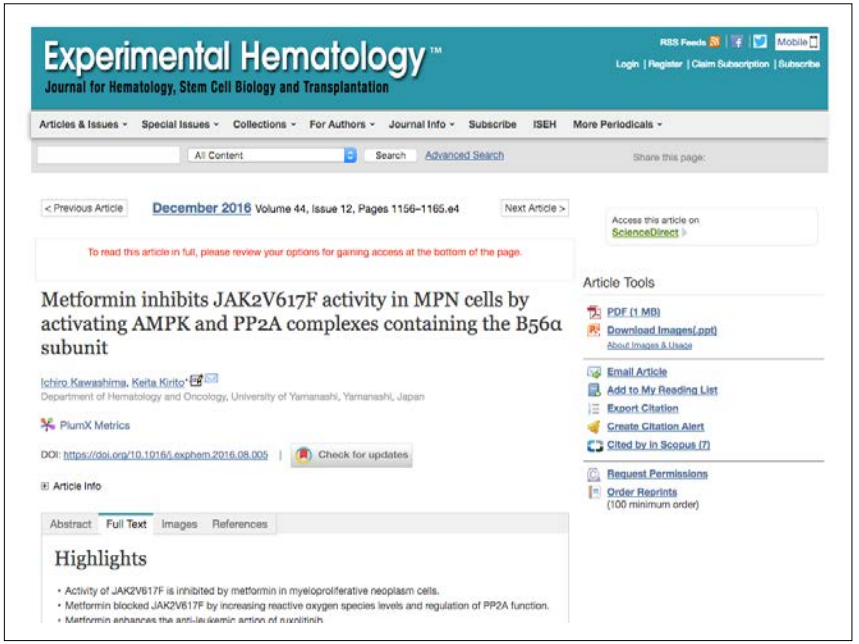
MetforminによるJAK2V617F活性制御



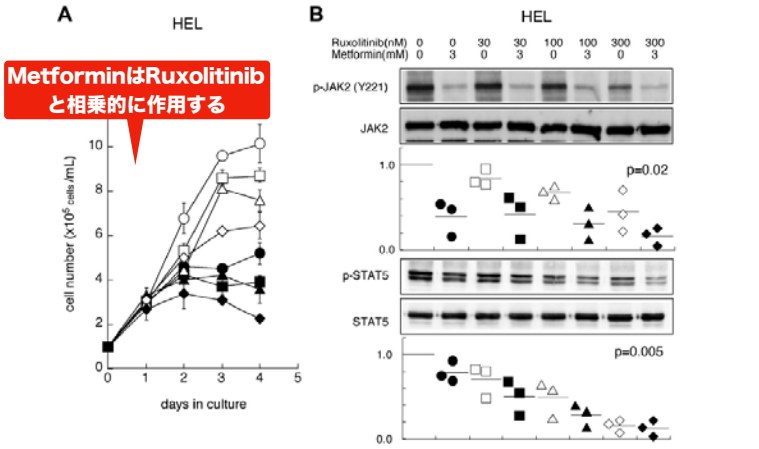
ストレス応答とMPN



3. MPN治療剤としての Metforminの可能性



MetforminとRuxolitinibの協調



Kawashima I et al. Exp. Hematol 2016, 44, 1156

MetfrominとMPN