ASH2025

文責：合山

Chiara Bonini

Gene Transfer and Genome Editing of T cells for Cancer Immunotherapy
HSCT の治療効果には GVL が重要 → Engineered T cell therapy の時代に
DLI Donor T cells + suicide gene (HSV-TK) → less GVHD
Challenge: HSV-TK-transduced HSC are short lived and immunogenic → CAR T cells
TCR gene Editing: very effective
Hunting for novel tumors associated antigen (TAA)-specific TCRs → Generation of TCR-T
Engineering T cells to hinder T cell immunosuppression at TME → CD39 depletion
TIM3-KO + WT1-TCR edited T cells control tumor growth
Base Editor can be used for T cell engineering
TIGIT gene disruption rescues the antitumor activity of low avidity engineered T cells

＊endogenous TCR を KO して、WT1 など TAA-specific TCR を導入する Engineered TCR-T の話がメイン。CAR-T と TCR-T、どちらが今後主流になるか？

Qian Zhang

Development of synthetic introns for selective elimination of U2AF1 mutant MDS
Aberrant 3'splice site usage by mutant U2AF1-S34 mutations
Harnessing U2AF1-S34 mutant splicing for therapeutic intent→HSV-(intron)-TK with intron
Improving specificity of U2AF1 mutant synthetic intron
129G>T promotes wild-type splice site recognition
confirmed the therapeutic effect using the in vivo K562 model:
cDNA screen with 12,000 variant intron
Double mutation (129/199) enhanced the efficacy
Delivery of synthetic introns as LNP-encapsulated plasmid DNA

＊U2AF1 変異で splicing pattern が変わることに注目し、変異を持つ細胞だけで splice される人工イントロンを自殺遺伝子(HSV-TK)に組み込むことで変異細胞だけで自殺遺伝子が ON になるシステムを開発。発想も面白いし、LNP を活用した実用化まで進めている。

Stefan Tarnawsky

Missplicing of Mdm4 activates TRP53 and impairs HSPC growth in a mouse Model of MDS
Why do U2AF1-S34F HSPC grow poorly?
U2AF1-S34F induces upregulation of TP53 target genes

Trp53 deletion partially rescues the growth of U2af1-S34F HSPCs.
U2af1-S34F induces a dysfunctional Mdm4 isoform in mouse HSPCs
Mdm4 overexpression partially rescues the impaired growth of U2af1-S34F HSPCs.
U2af1-S34F HSPCs are preferentially sensitive to TRP53 reactivation in vivo
質問：TP53 mutation や MDM4 amplification は U2AF1 mutation と共存するか？
A: Chr1 の amplification が多い。MDM4 は Chr1 にある。

＊U2AF1-S34F 変異細胞の増殖が悪い原因として、MDM4 の mis-splicing→p53 活性化を同定した研究。ただし、Trp53-KO による rescue は partially なので、それが全てでは無いだろう。

Omar/Fujino

Mitochondrial transplantation in the treatment of MDS
MDS: increased ROS and apoptosis, **Increased mtDNA mutation**
Allogenic healthy mitochondria could be safe and effective therapeutic resource
Ex vivo introduction of allogenic healthy mitochondria into patient CD34+ HSCs
Mouse model for MDS: NUP98-HOXD13(NHD13) transgenic mouse
MHD13 mice have impaired mitochondrial function
NHD13+MAT(mitochondrial augmentation：胎盤由来のミトコンドリアと混ぜる) suppressed leukemic transformation of NHD13 cells
CD34+ MDS cells impaired erythroid differentiation was rescued by MAT
Phase I: no safety problem, anemia was improved and a patient became transfusion independent

＊ミトコンドリアが細胞間で伝搬する性質を利用して、胎盤由来のミトコンドリアを MDS 患者の造血幹細胞混ぜることにより、MDS が改善したという驚きの結果。AML への移行を促進する懸念もあると思うが、マウスモデルではむしろ AML 発症を抑制している。low grade MDS に限る必要はあると思うが、興味深い。卒業生の藤野君の研究。

Sweta Patel

Targeting nicotinamide salvage pathway is a unique metabolic vulnerability of high-risk MDS stem cells
Healthy CD34+ vs HR(high risk)-MDS CD34+:
HR-MDS HSCs have increased mitochondrial respiration
HR-MDS HSPCs have increased proteins that use NAD+ for their function
No change for NAD+/NADH
NAMPT is the rate limiting step in the NAD biosynthesis pathway
OT-82: NAMPT inhibitor

HR-MDS HSPCs rely on NAMPT for their survival
NAMPT knockout inhibit the engraftment of MDS-L cells
質問への A: A previous paper showed that AMLs with chr 7q deletion are more sensitive to NAMPT inhibition.

＊NAMPT inhibitor は毒性が強すぎるのではないかと思っていたが、意外と使えるのかもしれない。

Maroof Hasan

Luspatercept reduces cardiac stress and improves cardiac function in a TET2-deficient mouse model with features of heart failure
Luspatercept: an inhibitor of activin receptor -Smad2/3 signaling
COMMANDS is a global phase3 trial for the treatment of anemia due to IPSS-R very low, low or intermediate risk MDS
High NT-proBNP levels were associated with common MDS-related mutations: TET2, SF3B1, ASXL1...
Decreased NT-proBNP in patients who achieved the primary endopoint
Hepcidin, associated with iron homeostasis and CVD, was also reduced in Luspatercept-treated Pts.
Heart Failure with preserved ejection fraction (HFpEF)-like mouse model +/- TET2 KO
HFpEF+TET2 KO: cardiac hypertrophy, which was reversed by RAP536 (mouse version of Luspatercept)

＊TET2, SF3B1, ASXL1 変異を持つ MDS では心機能も少し低下していることが多い。MDS による貧血治療で Luspatercept を使ったら、何と心機能まで改善したという話。機序は不明だが、macrophage などの悪い作用を抑えているのだろうか？

Mortiz Binder

Clone-specific epigenetic regulatory mechanisms in ASXL1-mutant chronic myelomonocytic leukemia
ASXL1 mutations are common in CMML
Epigenetic regulatory mechanisms in ASXL1-mT CMML: aberrant ASXL1-MT specific enhancers
BRD4 and p300 are recruited to activated enhancers
Single cell chromatin accessibility in ASXL1-MT CMML: more accessibility
EP31670 (BRD4/p300 inhibitor): preferential therapeutic effect in ASXL1-MT samples

＊ASXL1-mutant の遺伝子発現制御機序では、ASXL1 変異/BAP1 複合体によるヒストン H2A-

K119 の脱ユビキチン化が有名だが、BRD4/p300 もリクルートされて標的遺伝子発現上昇に関与しているという話。

Alison Maloney

MLLT1 (ENL) and MLLT3 (AF9) target protein degradation (TPD) for targeting the super elongation complex (SEC)

MLLT1/3 are histone reader proteins with a selective role in SEC mediated transcription control

MLLT-TPD lead to potent and selective degradation of MLLT1/3

MLLT1 localizes to small set of genes: HOXA9, MEDIS, RUNX1...

MLLT degradation strips the SEC from chromatin at specific loci (HOX cluster)

Loss of MLLT1 leads to downregulation of target genes

MLLT-TPD has broad activity to leukemia cell lines

MLLT-TPD has a more profound impact on SEC occupancy than MENIN inhibitor

MLLT-TPD, but not Menin inhibitor, inhibits MYC and RUNX1-RUNX1T1 expression

697 cells harboring E2A-PBX1 and Kasumi1 cells harboring RUNX1-RUNX1T1 are sensitive to MLLT-TPD but not to Menin inhibitor

MLLT-TPD is effective on primary AML cells and Menin-I resistant cel lines

MLLT-TPD is high effective and well tolerated in vivo

質問への A: normal HSPC には調べた範囲では大きな影響はない、とのこと。

＊MLLT1/3 degrader を開発し、効果を確認した研究。Menin 阻害剤よりも AML に対する効果は強そう。副作用があまりないというのが信じられないが....

Daniela Wenge

The KMT2A(MLL)-PTD oncoprotein depends on ENL but not Menin to drive AML gene expression

Endogeneous taggiong of KMT2A-PTD and KMT2A-WT in EOL-1 cells

Degradation of KMT2A-PTD, but not WT KMT2A, induced differentiation of EOL-1.

RNA-seq/SLAM-seq revealed target genes: HOXA9, HMX2, HMX3, CDKN2C, MYC and CDK6

KMT2A-PTD leukemia models show low sensitivity to Menin inhibition

The duplicated CXXC domain and AT hooks of KMT2A-PTD mediate retained chromatin binding of KMT2A-PTD even with MENIN inhibition

Both YEATS proteins, ENL and AF9 (MLLT1 and MLLT3), drive gene expression in KMT2A-PTD leukemia

YEATS and Menin inhibition synergistically inhibit KMT2A-PTD leukemia in vitro and in vivo

＊KMT2A(MLL)-PTD では、CXXC domain と AT hooks が duplicate されているぶん Chromatin

への結合が強く、Menin 阻害剤があまり効かないとのこと。むしろ ENL/AF9 に依存しているらしい。前の演題の MLLT1/3 degrader が効きそう。

Prateek Bhardwaj

Epigenetic silencing of O6-methylguanine-DNA methyltransferase (MGMT) occurs as a common DNA damage response (DDR) defect.
AML and low-grade glioma are the lowest MGMT-expressing tumors.
MGMT repairs O6-guanine alkylation damage, and its loss sensitize cells to alkylating agents.
Temozolomide showed modest efficacy on MGMT-silenced AML in previous clinical trials
Loss of mismatch repair (MMR) pathway drives resistance to TMZ in MGMT-silenced patients
KL50: A fluoroethyl TMZ analog targets MGMT-deficiency independent of MMR
MGMT-silenced AML cell lines are sensitive to TMZ and KL50
MGMT- silenced but not MGMT+ primary AMLs are sensitive to TMZ and KL50
R/R AML patients frequently show combined MGMT and MMR deficiency
MMR-deficiency renders MGMT-deficient isogenic cell xenografts resistant to TMZ but not to KL50
MMR mutations that occur in response to TMZ drive resistance to TMZ but not to KL50

＊MGMT という DNA 修復酵素の発現が低い AML が存在し、それにアルキル化薬である TMZ がよく効くが、MMR pathway gene の mutation が入るとすぐに効果がなくなるらしい。新しく開発された KL50 は、MMR に依存していないので、より効果的という話。

Divij Verma

Ofirnoflast, a novel inflammasome inhibitor, rewires transcriptional programs and shows efficacy in myeloid neoplasms
NEK7 is a critical adaptor for NLRP3 inflammasome
Ofirnoflast: NEK7 inhibitor that inhibits inflammasome formation
Increased inflammasome is often observed in CMML and MDS
Ofinoflast treatment inhibited the growth of MDS and CMML, **prevents inflammasome-mediated GATA1 cleavage, and induced erythroid differentiation.**
Activated inflammasome leads to increase of IL-1b.
Genetic depletion of IL-1R and Anakinra (IL-1b inhibitor) treatment abrogated the antileukemic effect of Ofirnoflast.
Phase I study: placebo vs ofirnoflast : decrease of inflammatory cytokines IL-1B, IL-28, IL-6, TNF-a.

＊インフラソーム inhibitor が MDS と CMML に効果的という話。AML はどうなのか？個人的に、**インフラソームが GATA1 の cleavage を誘導しており、それを阻害すると GATA1 が**

復活して分化誘導する、というメカニズムが興味深かった。

Gaston Soria

ONC001: ADC targeting CD64 for the treatment of monocytic leukemia
Monocytic cells (CMML+M4/M5 AML) are refractory to current treatments.
CD64: an emerging target for the treatment of monocytic leukemia
monocytic LSC: CD34-, CD117-, GPR56-, CD14-, CD11b- and **CD64+**
PNU-159682, a topoisomerase II inhibitor serving as a payload for antibody-drug conjugates (ADCs), exposes a unique vulnerability to target monocytic cells
A first in class CD64-ADC with high potency and selectivity was only effective for monocytic leukemia, triggers complete and durable remissions in vivo with no signs of systemic toxicity

＊Monoctyic AML の LSC marker として CD64 を使い、CD64-ADC の効果を示した研究。CD64 は他の細胞では発現していないのか？

Grant Challen

Dnmt3a-mutant HSC; high expression of TERT, longer telomere
Loss of Terc inhibits expansion of Dnmt3a mutant HSCs
JAK3-V617F host support the growth of TET2-mutant cells
MPN cytokines promote the growth of TET2-mutant cells

＊前半は、DNMT3A 変異を持つ HSC では Teromerase 活性が亢進し、テロメアが長く、これが HSC の増殖(クローン性造血の促進)に重要という話。なぜ DNMT3A 変異がテロメレース活性を上げるのか、機序はまだわかっていない。後半は、TET2 変異細胞が炎症環境化で増えるという話で、最近のトピック。CH の進展には、mature な細胞や微小環境が作る炎症状態が重要というコンセプトは確定した感がある。

Michael Milsom

Inflammatory stress (8x pIpc x3) induced **irrreversible** depletion of HSCs even after 20 weeks
Inflammation drives proliferation of dormant label retaining cells
Proliferation, not systemic inflammation, inhibits HSC function
pIpC increase the biological age
Exit from dormancy increase the DNA damage in HSCs
Dormancy restricts the age associated mutagenesis in HSCs
Inflammation accelerates mutation acquisition in HSCs
Inflammation mediates irreversible depletion of HSC pool, and accelerated HSC mutagenesis

＊炎症 → HSC 増殖 → DNA damage → 変異獲得、という流れとのこと。
CH モデルで同じように pIpC を打つとどうなるか？

Nancy Gillis

Clonal Hematopoiesis
CH: any gene, any VAF
CHIP: myeloid gene, VAF>2%
risk factors for CH: HIV, hypertension, smoking
CH is associated with decreased risk of AD, and CH variants are detectable in microglia
TET2-CH is associated with reduced risk in a mouse model, but other CH drivers are not.
CH increases risk of AD with APOE e3/e3 genotype (前の報告と反対)
In allogenic HSCT, donor CH may have protective effects: 20% dicrese of risk of relapse
DNMT3A-CH reduces relapse risk, while TET2-, and ASXL1-CH increase the risk of relapse
CH increases the CVD risk and toxicity of CAR-T therapy
Increase of CH clone during the therapy, but not the presence of CH prior to therapy, is associated with outcome of breast cancer patients
CHIP increase with age -10T of 70 year
Splicing mutations, high VAFs and more mutations increase the risk for adverse outcomes
Most patients with CHIP will not progress to myeloid neoplasms
High risk patients (1.1 %) should be monitor more frequently

＊CH、CHIP の疫学研究。いつどのように介入するかは難しい問題。CH(clonal hematopoiesis) と CHIP のこの定義はわかりやすい。

Irenaeus Chan

CDK4/6 inhibition mitigates chemotherapy induced expansion of TP53-mutant CH
CDK4/6 reduces HSCs cycling
Trilaniclib reduced chemotherapy-induced anemia and thrombocytopenia
Rondamized trial for SCLC(肺がん): Chemotherapy +- Trilanilib
Trilaciclib decreases detectable DDR mutations after the therapy
CDK4/6 inhibitors protects Trp53-WT HSCs wile potentially promoting apoptois of Trp53-mutant HSCs

＊TP53 変異細胞は、意外にも定常状態ではそんなに増えないが、固形腫瘍に対する化学療法後に増殖して、難治性の tMN になることが知られている。HSC の増殖を抑制する CDK4/6 阻害剤を化学療法中に加えるだけでこれを抑制できるという話。言われてみればなるほど

で、臨床に応用できそう。またこれは、CDK4/6 に反応しないタイプの血液腫瘍治療にも使えるのではないか？

Yang Feng

Inhibition of DOCK1 prevents the clonal expansion of high-risk TP53 mutant CH induced by genotoxic stressors

TP53-mutant CH model: introduced mutation into primary human HSPCs using CRISPR/AAV-mediated homolgy-directed repair.

TP53-KO HSPCs showed increased self-renewal upon paclitaxel and olaparibin treatment both in vitro and in vivo

Mining Synthetic lethal (MiSL) analysis identified DOCK1 as a predicted synthetic lethal target in TP53-mutant AML cells.

Co-depletion of DOCK1 inhibits the colony formation of TP53-KO cells in Olaparib-containing culture

Transient pharmacological inhibition of DOCK1 ameliorates the colony number of TP53KO HSPCs upon paclitaxel or olaparib treatment

＊最後の DOCK1 阻害剤の実験では、TP53-KO 細胞が完全に死ぬわけではなく、少し減るだけなので、"synthetic lethal"とまでは言えないのでは？MiSL は使ってみる価値あるかも。

Masahiro Nakagawa

Bone Marrow environmental alteration underlies proliferative clonal expansion in CHIP

scRNAseq + genotyping

CHIP mutant cells: more proliferation, less inflammation

Aged bone marrow: more inflammatory environment

Bone marrow environment is inflamed in CH+ cases

Mouse model to mimic human CHIP: Tet2+/- + WT cells

Mutant cell may exert non cell autonomous effect

Mild IFNa mimics noncell autonomous effects and promotes the growth of TET2-CHIP

＊CHIP 変異があると BM が炎症気味になり（たぶん CH 変異+マクロファージなどの影響)、普通の HSC は damage を受けるが CHIP 変異 HSC は平気なので増殖優位性を持つという話。ASXL1-mutant 細胞は pIpC 投与で減った記憶があり、詳しく調べる価値があるかも。

Taishi Yonezawa

Dissecting how pulmonary remodeling from cigarete smoke impacts CH

COPD is associated with CH
Emphysema is one of the major components of COPD
ASXL1 mutations are associated with smoking
Examine the link between ASXL1 mutations CH and smoking
nCB (carbon black) treatment induced ASXL1 mutations in mouse model
nCB treatment in Asxl1 mutant mice enhances CSF (G-GSF and GM-CSF) production and inflammatory responses
nCB also increases the number of monocytes and inflammatory monocytes → promotes the onset of CMML

＊Smoking で ASXL1 変異が増えることは疫学研究でわかっているが、それがマウスモデルでも再現できることを証明。なぜ TET でも DNMT3A でもなく、ASXL1 が smoking で増えるかはよくわからないが、マウスモデルで再現したことの意義は大きい。**理由に迫る研究をこちらでできないか**？卒業生の米澤君の発表。

Guangshuai Teng

JAK2-V617F increases susceptibility to atrial fibrillation via NLRP3 inflammasome activation in macrophages
AF induction rate is significantly increased in JAK2-V617F mice
Left atrial fibroblast activation in JAK2V617F mice
High expression of collagen 1, CCR2+ macrophages in JAK2 mice
CCR2+ macrophage: high NLRP3, IL-1b
Macrophage inflammation activates fibroblast
Ruxolitinib reduces AF incidence in JAK2-V617F mice

＊JAK2-CHIP は Af とも関連しているらしい。

Kelly Bolton

Ivosidenib leads to durable responses in IDH1 mutated clonal cytopenias of undetermined significance (CCUS)
Ivosidenib blocks production of 2-HG and prevents the development of IDH1-mutant AML
Most CCUS patients have co-occuring spliceosome mutations
90% of patients had hematologic response to Ivosidenib with rapid and sustained response
95% patients slow decline of IDH1-mutant cells
Mutational evolution commonly observed (6/20)
Ivosidenib inhibits cytopenias and autoimmune diseases

＊確かに、IDH 阻害剤は CCUS などを対象に早めに使ってもいいかもしれない。

Marta Derecka

Malignant cells remodel BM niche: less supportive cytokine, increased inflammation
Blood Transcription factors are expressed in BM niche: Ebf1 and Runx1
EBF1 is expressed in LepR+ MSCs
Ebf1f/f + Prx1-cre → Ebf1-deficient MSCs: reduction of HSCs and Myeloid cells
HSCs in Ebf1-deficient MSC mice: more apoptosis, less cell cycling, less myeloid output, and showed increased sensitivity to 5-FU: reduced regenerative capacity
The HSCs have reduced multilineage engraftment in secondary mice (なぜ 2nd だけ?)
Decreased Number of quiesent HSCs in Efb1 deficient niche: more Malat1, less CDK6
Reduced occupancy for myeloid TFs motifs in HSCs from Ebf1-KO niche
Reduced expression of Adhesion genes in Ebf1-deficient MSCs
EBF1 is expressed in pre-fibrotic LepR+ MSCs
EBF1 is upregulated in mouse MF (myelofibrosis) niche
EBF1 is increased in humna MSCs coculture with MF CD34+ cells
MSC-specific Ebf1 deficiency reduced myelofibrosis driven by MPL-W515
EBF1 regulates fibrotic gene expression program in human MSCs
EBF1 binds fibrotic genes and Itgb8 is a direct target gene of EBF1
ITGB8 neutralizing antibodies alleviate MF, reduce BM inflammation and Fibrotic markers
Itgb8 depletion in MSCs reduces MF cell expansion and BM fibrosis

＊MSC における転写因子の役割はほとんど知られていないので、ここに注目したのは面白い。しかし転写因子は治療標的にしにくいので、結局その標的遺伝子である ITGB8 標的治療に戻っている。

Leif S Ludwig

Mitochondrial DNA mosaicism and clonality in human hematopoiesis
Clonal tracing via somatic mitochondrial DNA (mtDNA) mutations
Increasing mitochondrial DNA mosaicism with age
Most somatic mtDNA variation only arises after development (no mutation in Cord blood)
Limited evidence of mitochondrial transfer following transplantation (少しはあるが、少数)
Purifying selection of pathogenic mtDNA in human T cells

＊ついに CH 研究はミトコンドリア変異に注目する時代に突入した模様。

Eirini Trompouki

RLRs: RIG-I, MDA5, LGP2
Reduction of inflammatory cytokines in MDa5-KO BM serum
MDA5 loss reduces HSC/MPP expansion during aging
MDA5-KO HSCs are more quiescent than WT during aging
Enhanced repopulation capacity of aged Mda5-KO HSCs
Less aging signature in Mda5-KO HSCs
Translation and Proteostasis is up in Mda5-KO HSCs,
HSF1 is increased and PERK signal increased in Mda5-KO HSCs
Aged Mda5-KO HSCs have increased phospho-EIF2a
Mda5-/- HSC produce less protein
HSF1 activator treatment mimics the phenotype of Mda5-KO mice
MDA5 keeps HSC1 out of nucleus
Mda5-KO mice exhibit younger characteristics
Loos of Mda5 delays the aging in HSCs through active HSF1

Senescence: p16/GFP+ reporter mice
Some mice are bone with Green
Double stranded dsRNAs and Line1 are enriched in p16 high oocytes
Transposable elements (TEs) are upregulated in mouse p16 high oocytes
Humans have also p16 high oocytes
Enhanced TE expression and STING activation persist in adult
p16 activation is liked with cGAS-STING activation in p16REC mice

＊前半は、自然免疫経路を off(Mda5 KO)にすると造血幹細胞の機能が増強し若返るという話。ただ免疫能を抑制してしまうので臨床への応用は難しいか。後半は senescence との関係で、よく理解できなかったが、p16-high の卵母細胞があり、STING 経路が活性化されて、その影響が成長後も残るらしい。

Bruno Di Stefano

RNA condensates in leukemia and HSCs
P-body: DDX6, 4E-T, EDC4
RNA condensates are dysregulated in AML patients
more P-bodies in AML than HSCs
DDX6 serves as a genetic tool to modulate P-body assembly
P body disruption (DDX6 depletion) promotes differentiation

GFP-LSM14A as a marker of P-bodies
In AML, P-bodies sequester mRNAs encoding for tumor suppressors
DDX6 is dispensable for homeostatic hematopoiesis
DDX depletion expands phenotypic HSCs
DDX6 KO HSCs show loss of quiescence
Loss of DDX6 impairs the ability of HSCs to resist stress
P-bodies are required for muscle stem cell mediated regeneration
Lsm14a-GFP mouse to monitor P-bodies
miRNAs sequester their mRNA targets in P-bodies

*P-body (たぶん LLPS で形成される非膜構造体の一つ）が、tumor suppressor gene がコードしている mRNA を集める働きをしており、これが失われると造血幹細胞の quiescence が失われ、ストレス耐性が低下するとのこと。

Brandon Gheller

Pholphatidylcholine (PC) synthesis inhibition diminished ASXL1 and DNMT3a mutation driven CH
Two choline metabolites, betaine and acetylcholine, are reduced in CH clones
These changes can reflect increased partitioning of choline into phospholipid biosynthesis
PC is enhanced in dominant HSPC clones
PC generation is enhanced in human ASXL1-mutant HSPCs
CHKA inhibition reduces clonal expansion 2 months after treatment
Expression of a catalytically dead CHKA prevents Asxl1-mutant driven clonal expansion
CHKAi reduces expansion of TET2-mutant and DNMT3a-mutant cells
LPCAT2 catalyzes platelet activating factor (PAF) synthesis and has increase expression
PAF is sufficient to rescue the CHKAi's effect
CHKAi reduces expansion of ASXL1-mutant HSPCs
Enhanced phosphatidylcholine metabolism is a targetable metabolic vulnerability to prevent CHIP progression

＊PC 合成阻害剤は、CHIP の進展予防に使えるなら、monocytic AML の治療標的にしても良い気がしてきた。Monocytic AML で PC が増えているみたいな data が取れないか？

Marie Dominique Filippi

Mitochondrial antiviral signaling protein (Mavs) mediates inflammatory memory in HSCs and promotes ineffective hematopoiesis
dsRNA (pIpC) causes long-term HSC transcriptional and epigenetic changes

dsRNA challenge expands an HSC subset with immune memory
Mitochondria are platform of innated immune signaling
dsRNA activates mitochondrial antiviral signaling pathway
MAVS mediates dsRNA-induced responses
MAVS-/- HSCs retain superior engraftment capacity in serial competitive transplantation
MAVS deficiency prevents HSC immune memory and the development of MDS-like disease
MAVs contributes to inflammation driven defective hematopoiesis

＊MAV KO も inflammation が誘導する造血幹細胞の機能低下を防ぐ効果があるとのこと。免疫能低下のことを考えなければ、自然免疫経路の抑制は造血幹細胞機能を保つために極めて有効そう。しかし、実臨床で使えるか？

Devyani Sharma

Lipid deregulation impacts HSC functions during aging
Aged HSCs have abnormal lipid composition and more lipid storage
Cardiolipin (CL)decrease in Aged HSCs
Aged HSC have more lipid droplets
Mitochondrial-Lipid Droplet connection is lower in aged HSC
Aged HSC demonstrate lack of lipid incorporation
TAZ catalyzes CL remodeling into its mature form, which is required for maintaining mitochondrial functions
Mitochondira in TAZ KO HSC have abnormal lipid incorporation
TAZ KO mice have reduced HSCs, abnormal hematopoietic recovery after 5FU (reduced platelet, increased WBC)
Lower engraftment of TAZ-KO HSCs only in 2ndary recipient mice
AIcar (promote CL production) supplementation restores mitochondrial network and aged HSC transcriptome.

*HSC の脂質組成も老化によって変化(Cardiolipin が減る）し、それによってミトコンドリア機能が低下するらしい。

Baosen Jia

TET2 mutations drive cell autonomous type I interferon production and selective advantage through TRIM4 silencing
Isogenic human iPSC models of DNMT3A, TET2, ASXL1 mutations
TET2-mutant cells have markedly increased IFN signaling pathway, produce more IFN-I.

IFN-I, produced by TET2-mutant cells, suppress WT HSPCs, but TET2-mutant HSPCs are less sensitive to IFN-I.
TET deficiency silences E3 ligase TRIM4 in human HSPCs through enhanced promoter methylation
TRIM4 deficiency phenocopies TET2 deficiency
TRIM4 silencing unleashes IFN-I expression through decreased ubiquitination of DHX58 (a positive regulator of MAVs).
TET2 KO CB HSPCs have a competitive advantage, confers in vivo clonal advantage
TRIM4 deficiency also confers in vivo clonal advantage
TRIM4 overexpression ammoniates the clonal advantage of TET2-mutant cells

*中川先生の story と似ているが、target として TRIM4-DHX58 pathway を同定している。ここでも自然免疫経路が重要のよう。

Francesca Luca

Perturbation of iNKT differentiation during clonal hematopoiesis from rewiring of inflammation and lipid presentation
Tet2 deficiency modulated CD1d expression and Lipid antigen profiles in K562 and mouse cells
Tet2 loss induces myeloid skewing and disrupt peripheral iNKT homeostasis
Tet2-CHIP driven inflammatory environment (such as high IL-6) promotes overactivation of INKT cells and iNKT17 differentiation
TET2 loss resulted in alteration in endogenous glycolipid composition, changing the antigenic landscape.

＊TET2-CHIP の存在が、炎症性の環境と脂質抗原を変化させて、iNKT 細胞の機能を低下させるという話。ASXL1-CHIP ではどうだろうか？