Emerging Immune-related therapies in MDS/AML

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Disclosures

I have no relevant financial relationships to disclose

Overview

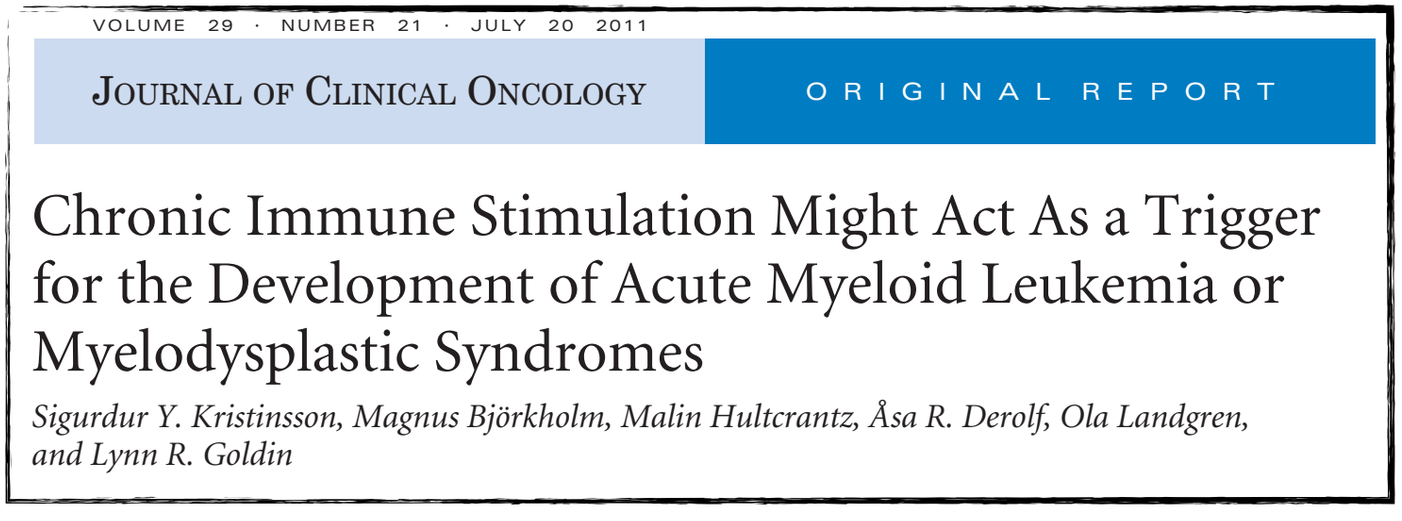
- Genetic and molecular mechanisms contributing to dysregulation of immune pathways in MDS.

- Epistasis between miR-146a and TIFAB, two genes in del(5q) MDS.

- Proof-of-concept and pre-clinical data on emerging immune-related therapies in MDS.

Aberrant immune function is a hallmark of MDS

- Increased inflammatory cytokines and chemokines:
  - *IL-1, IL-6, TNFa, IFNg, TGFb*
- Overexpression of immune receptors and ligands:
  - *TLR1/2/4/6, Alarmins/DAMPs (S100A8/A9, circulating DNA)*
- Altered immune cell populations:
  - *Regulatory T cells, Myeloid-derived suppressor cells*
- Associated with autoimmune and inflammation disorders:
  - *Rheumatoid arthritis, Inflammatory bowel disease.*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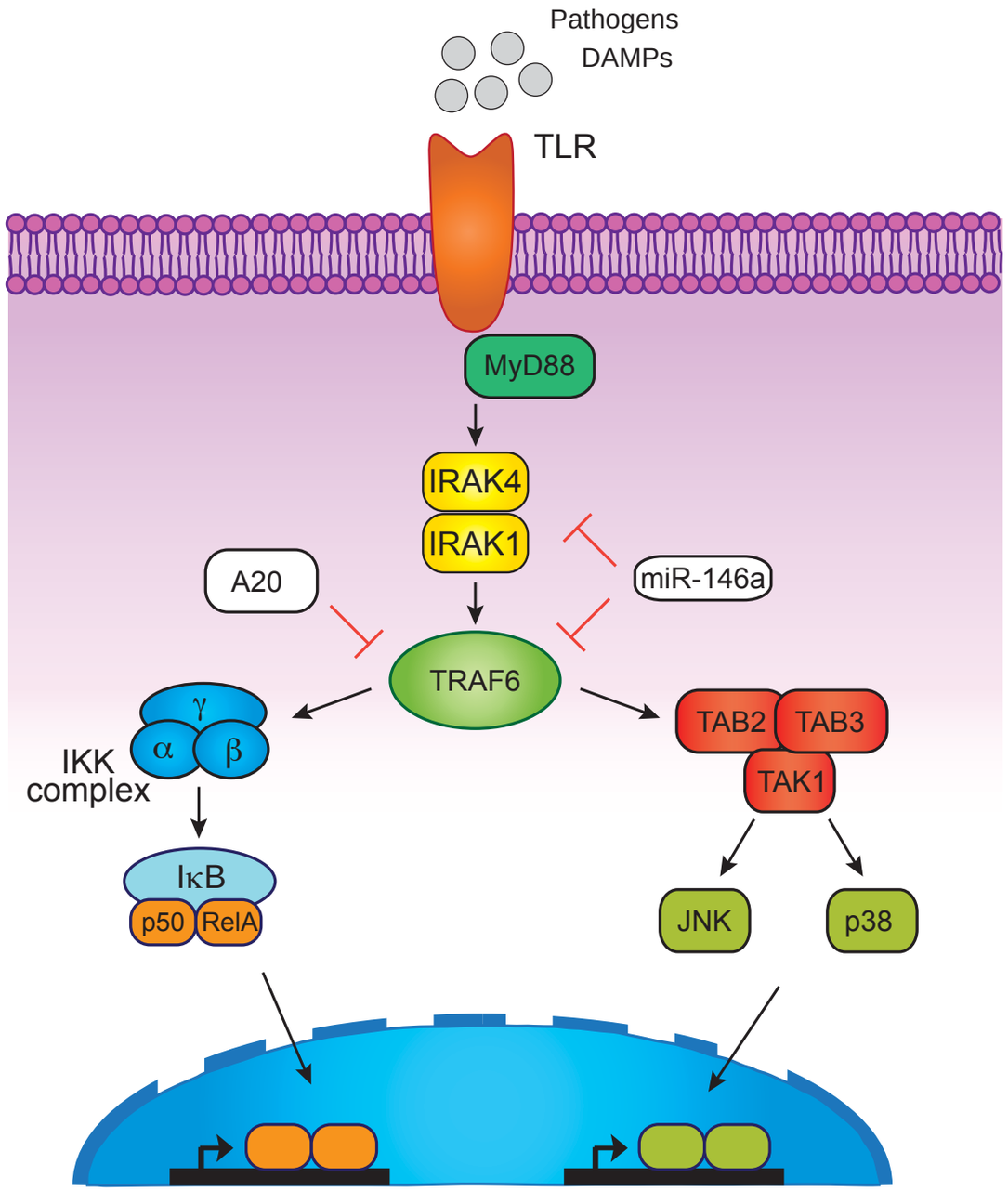
JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Chronic Immune Stimulation Might Act As a Trigger for the Development of Acute Myeloid Leukemia or Myelodysplastic Syndromes

Sigurdur Y. Kristinsson, Magnus Björkholm, Malin Hultcrantz, Åsa R. Derolf, Ola Landgren, and Lynn R. Goldin

Reviewed in: Ganan-Gomez, Starczynowski, Garcia-Manero, Leukemia (2015)

Innate Immune System: Toll-like receptor (TLR) signaling in immune effector cells



Cytokines

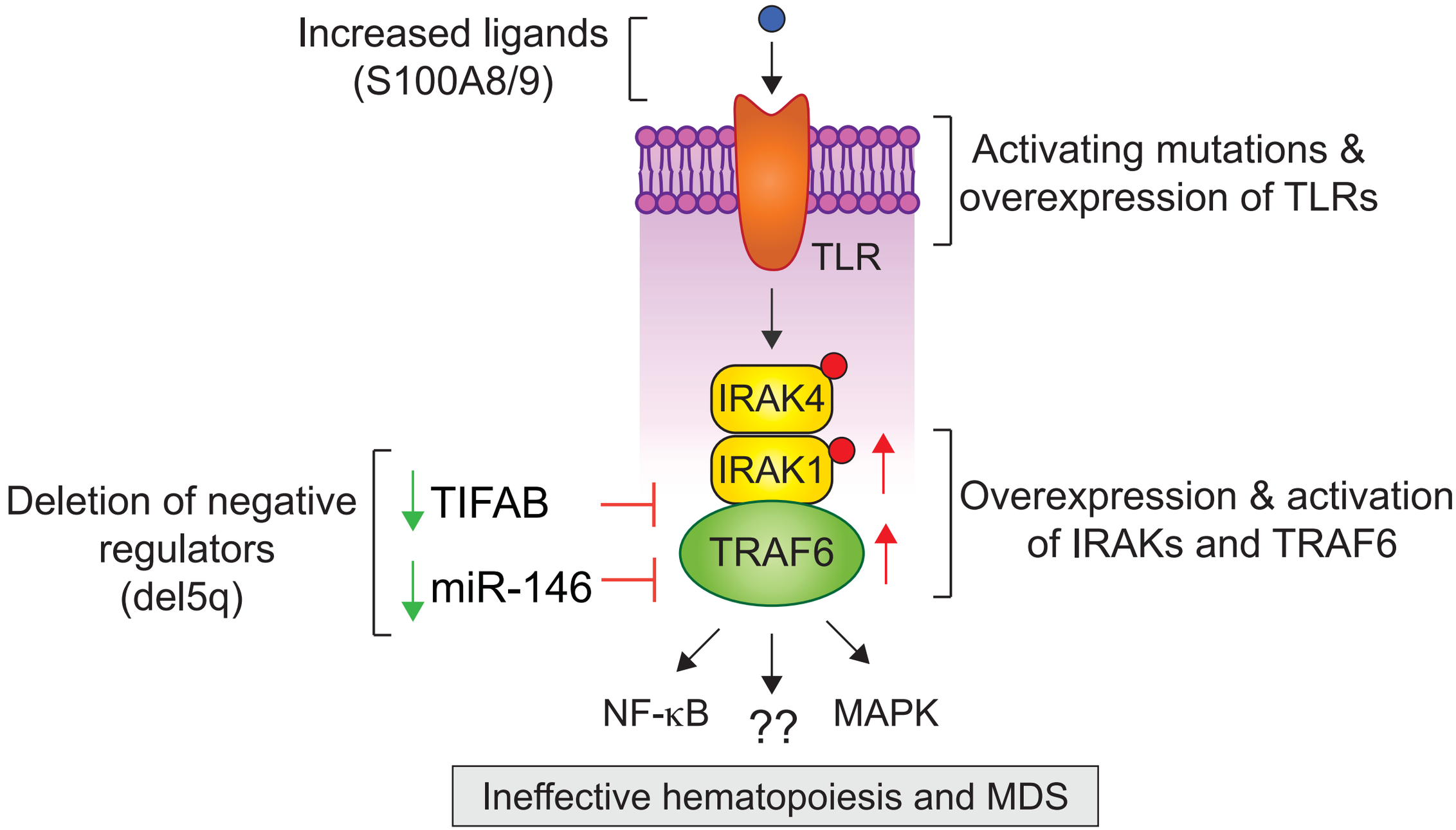
Cell proliferation

Chemokines

Differentiation

Anti-microbials

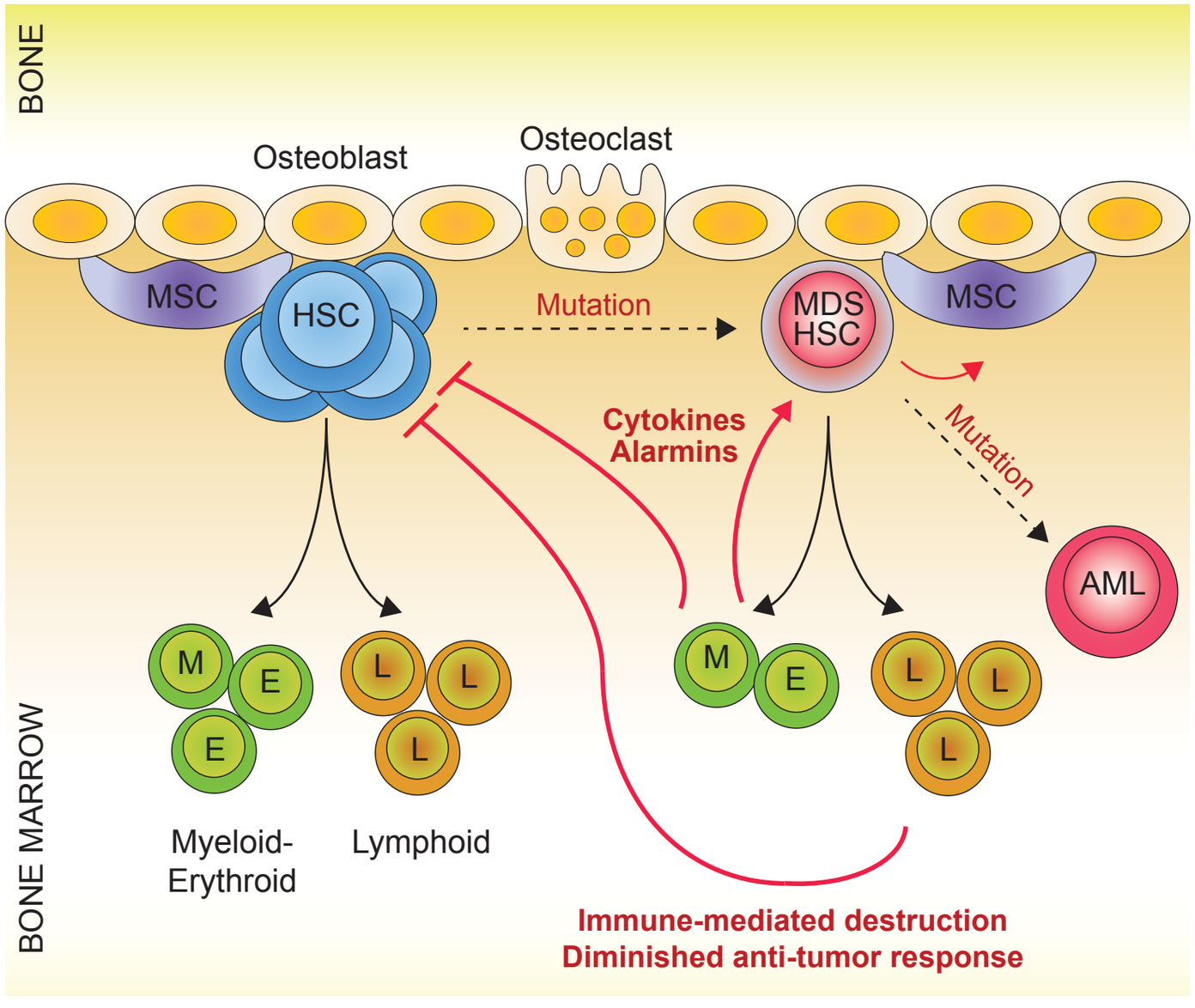
Multiple genetic and molecular mechanisms contribute to hyperactivation of TLR signaling in MDS HSPC



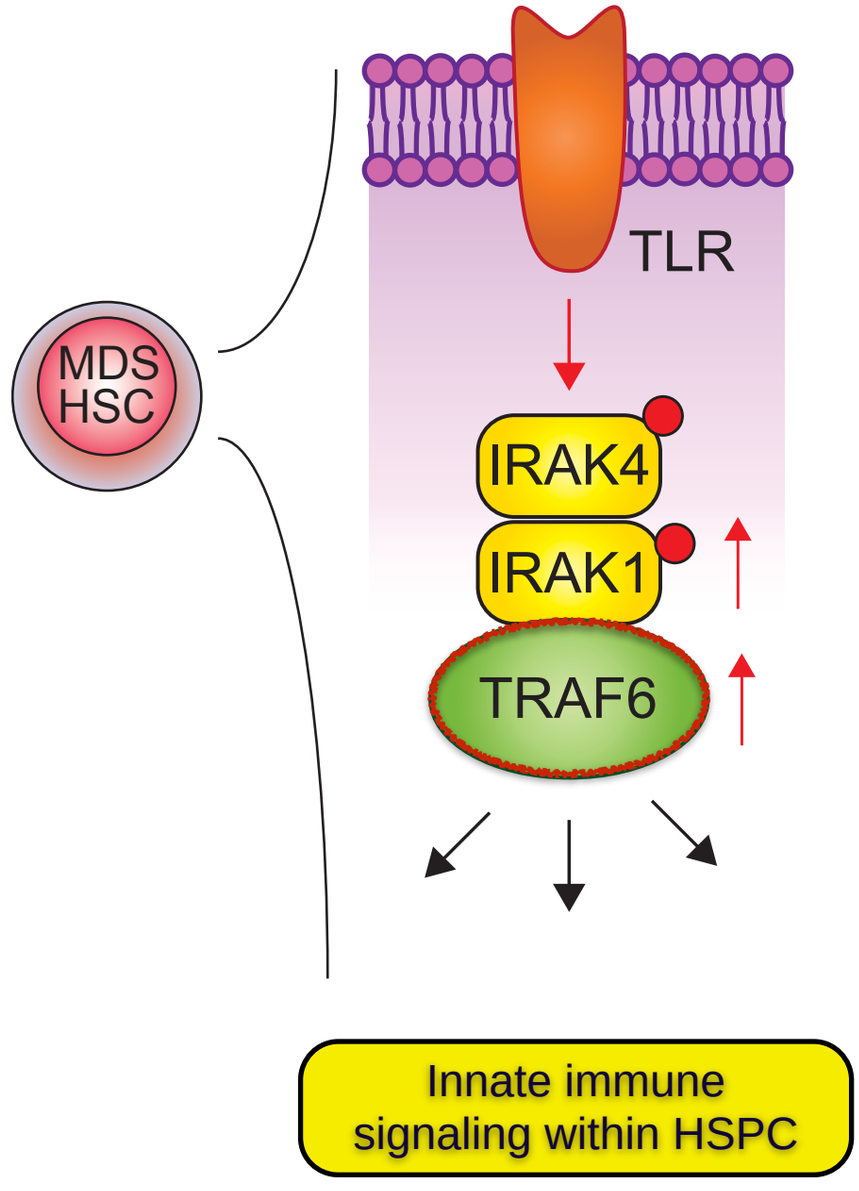
1. Hoffmann, et al., Blood (2002)
2. Starczynowski, et al., Nature Medicine (2010).
3. Wei, et al., Leukemia. (2013).
4. Varney et al., JEM (2015).
5. Schneider et al., Nature Medicine (2016).
6. Chen et al., JCI (2013).

Immune signaling contributes to hematopoietic defects and MDS by cell extrinsic and intrinsic mechanisms

Reactive/Cell Extrinsic

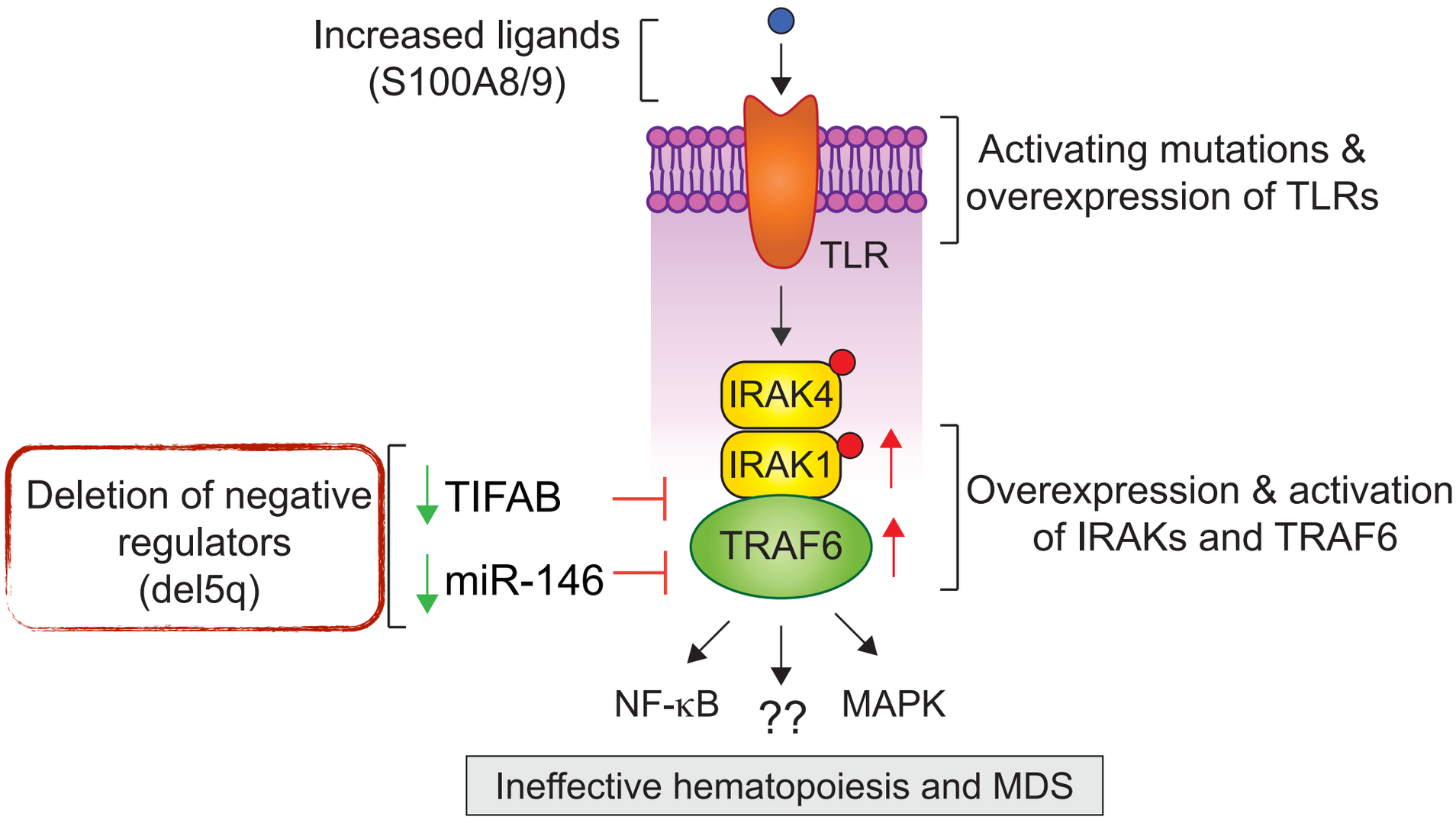


HSPC Intrinsic



Ganan-Gomez, Leukemia (2015); Yang, Cell Mol Life Scie (2015)

Why do MDS cells exhibit increased TLR signaling and what are the hematopoietic consequences?



miR-146a and TIFAB, two del(5q) MDS genes, restrict the TLR pathway in HSPC

nature medicine

Identification of miR-145 and miR-146a as mediators of the 5q– syndrome phenotype

Daniel T Starczynowski[1,2], Florian Kuchenbauer[1], Bob Argiropoulos[1], Sandy Sung[1], Ryan Morin[1], Andrew Muranyi[1], Martin Hirst[1], Donna Hogge[1], Marco Marra[1], Richard A Wells[3], Rena Buckstein[3], Wan Lam[1,2], R Keith Humphries[1,4] & Aly Karsan[1,2]

Cell Reports

Myeloid Malignancies with Chromosome 5q Deletions Acquire a Dependency on an Intrachromosomal NF-κB Gene Network

Jing Fang,[1] Brenden Barker,[1] Lyndsey Bolanos,[1] Xiaona Liu,[1] Andres Jerez,[2] Hideki Makishima,[2] Susanne Christie,[1] Xiaoting Chen,[3,4] Dinesh S. Rao,[5] H. Leighton Grimes,[1,6] Kakajan Komurov,[1] Matthew T. Weirauch,[3,7] Jose A. Cancelas,[1,8] Jaroslaw P. Maciejewski,[2] and Daniel T. Starczynowski[1,9,*]

JEM

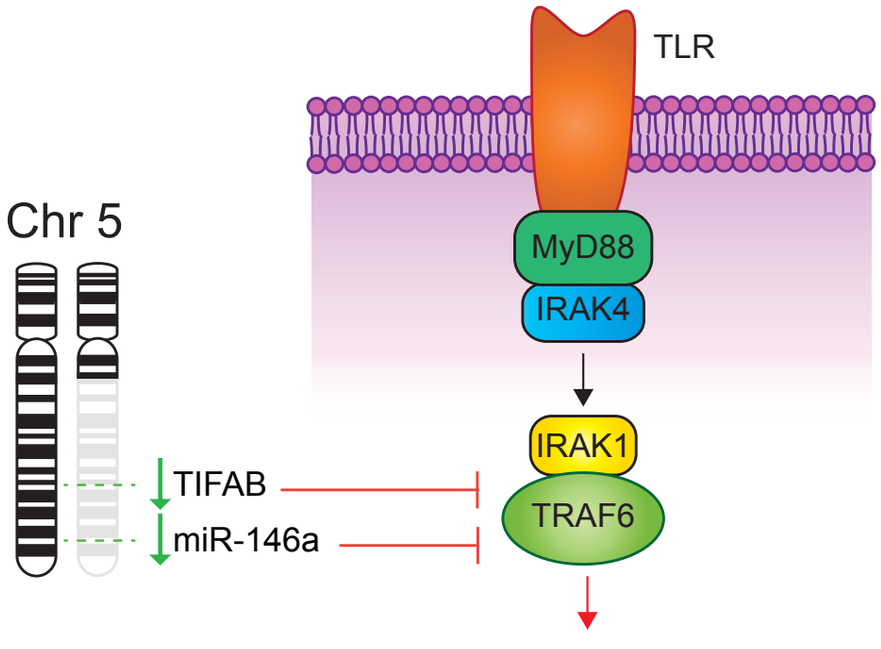
miR-146a is a significant brake on autoimmunity, myeloproliferation, and cancer in mice

Mark P. Boldin,[1,2] Konstantin D. Taganov,[1,2] Dinesh S. Rao,[1,3] Lili Yang,[1] Jimmy L. Zhao,[1] Manorama Kalwani,[1] Yvette Garcia-Flores,[1] Mui Luong,[1] Asli Devrekanli,[1] Jessica Xu,[2] Guizhen Sun,[2] Jia Tay,[2] Peter S. Linsley,[2] and David Baltimore[1]

JEM

Loss of *Tifab*, a del(5q) MDS gene, alters hematopoiesis through derepression of Toll-like receptor–TRAF6 signaling

Melinda E. Varney,[1] Madeline Niederkorn,[1,2] Hiroyasu Konno,[3] Takayuki Matsumura,[3] Jin Gohda,[3] Nobuaki Yoshida,[4] Taishin Akiyama,[3] Susanne Christie,[1] Jing Fang,[1], David Miller,[1] Andres Jerez,[5] Aly Karsan,[6,7] Jaroslaw P. Maciejewski,[5] Ruhikanta A. Meetei,[1] Jun-ichiro Inoue,[3] and Daniel T. Starczynowski[1,8]



miR-146a deficiency:

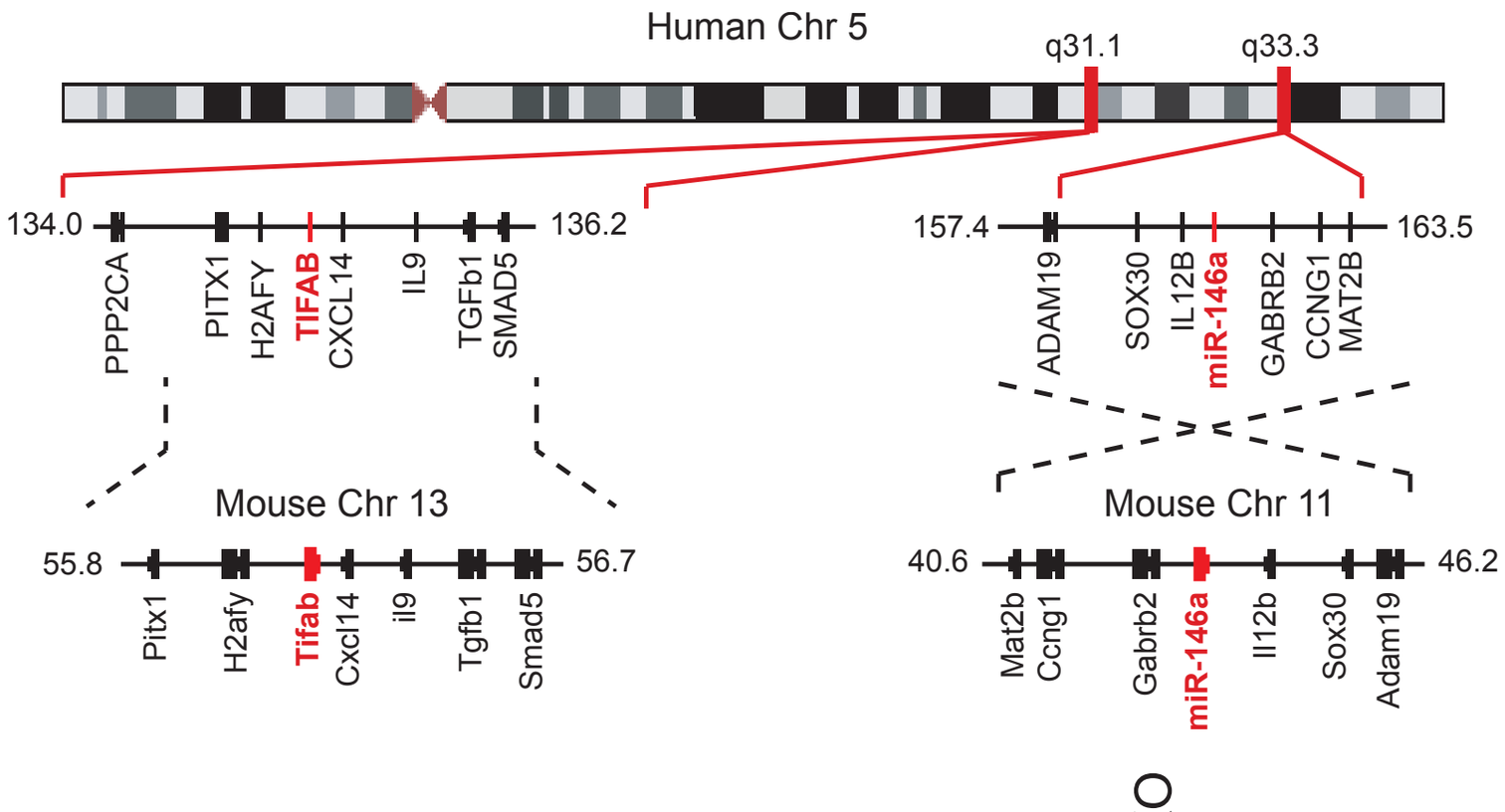
- Transient myeloproliferation/BM failure/MDS
- Altered hematopoietic stem and progenitor cell function
- Increased TRAF6 and IRAK1 mRNA stability
- Sensitive to TLR activation

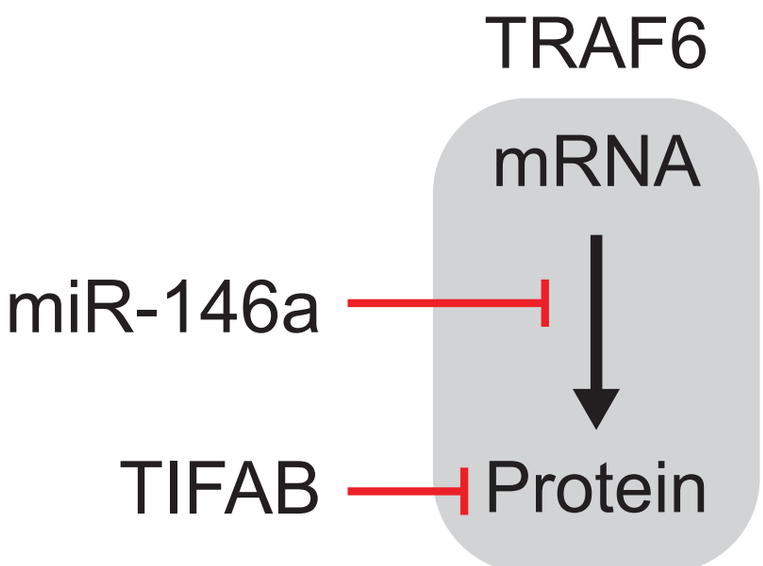
TIFAB deficiency:

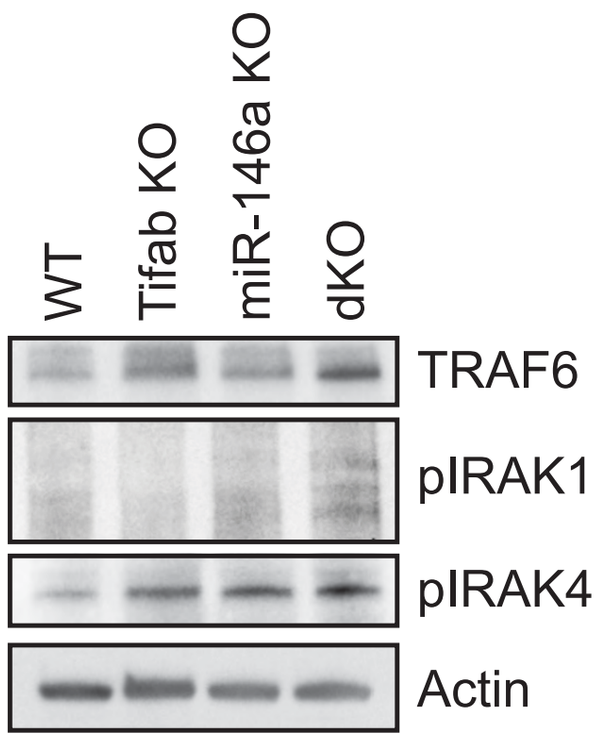
- Peripheral blood cytopenia
- Altered hematopoietic stem and progenitor cell function
- Derepression of TRAF6 protein
- Sensitive to TLR activation

Reviewed in Zhao and Starczynowski, Frontiers (2014)

miR-146a and TIFAB, neighboring 5q genes, cooperate to regulate TRAF6 and IRAK1/4

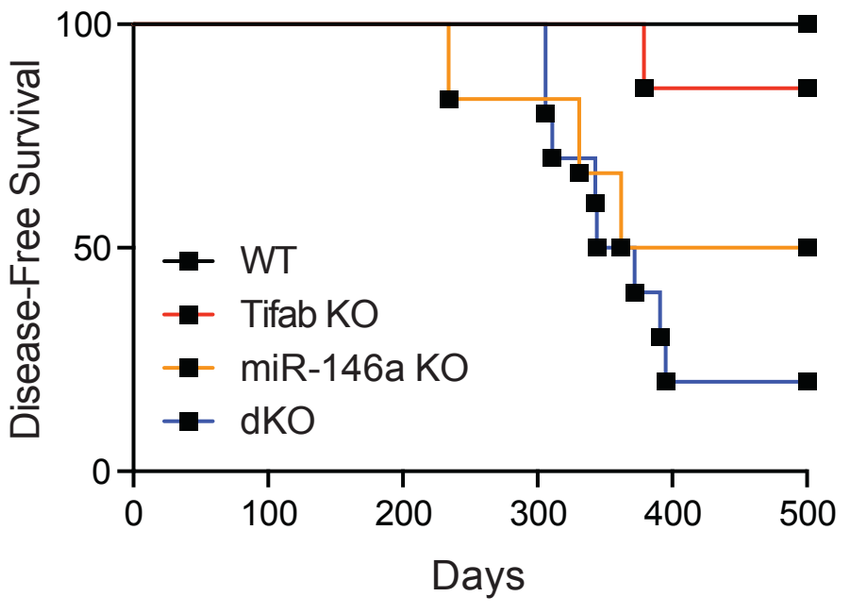


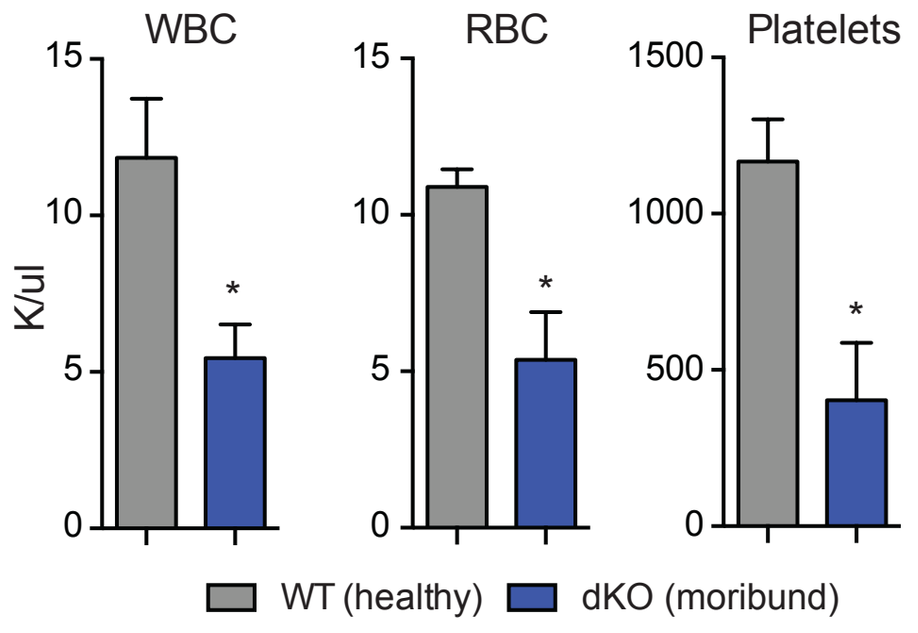


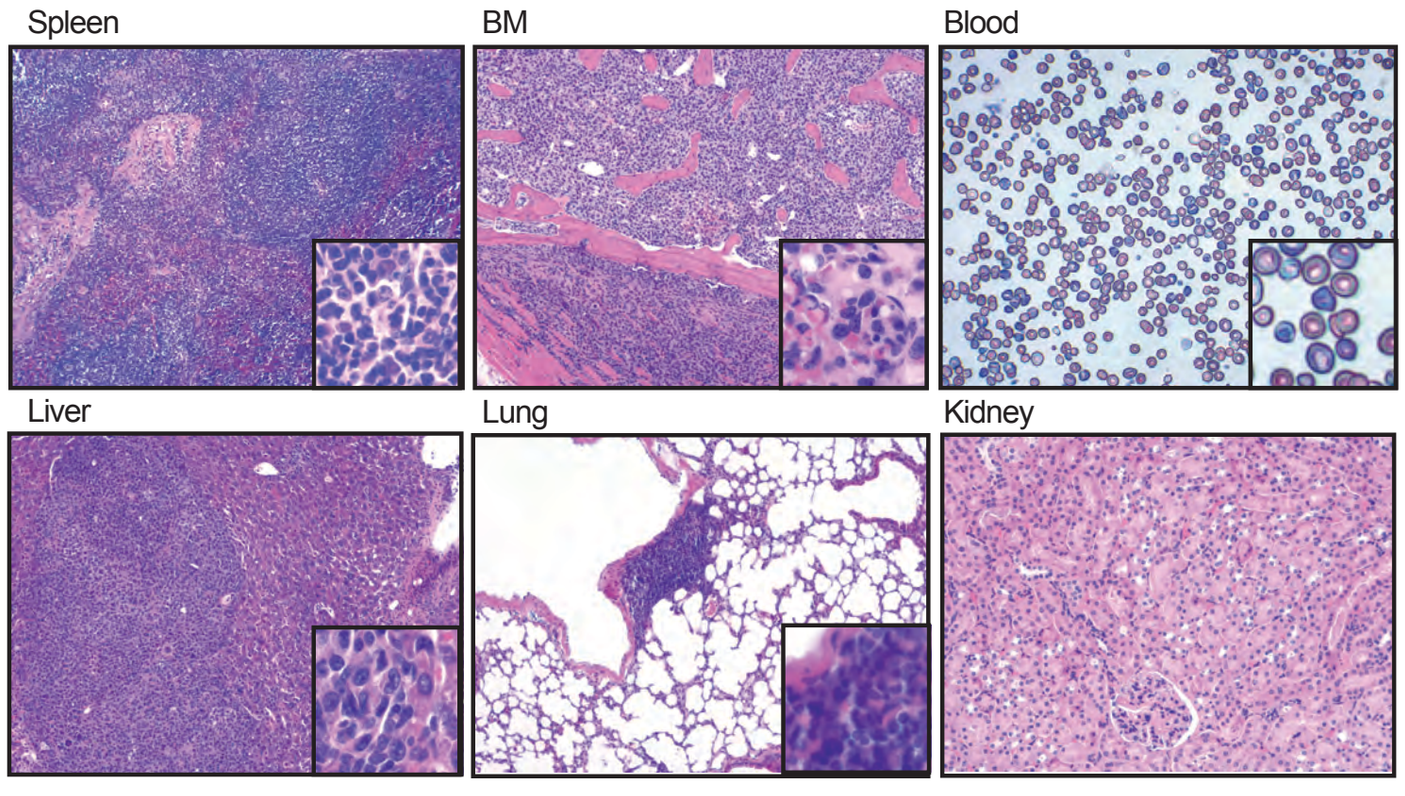


Varney et al., Leukemia (2016)

Deletion of miR-146 and TIFAB increases the severity of hematologic defects

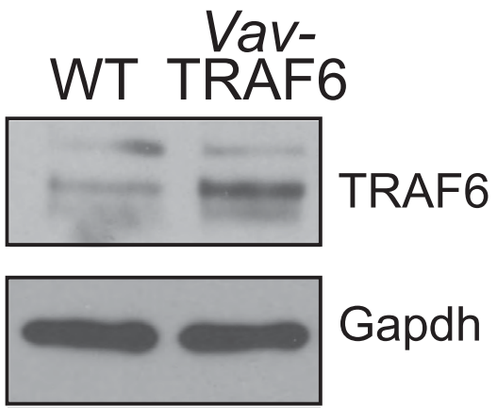


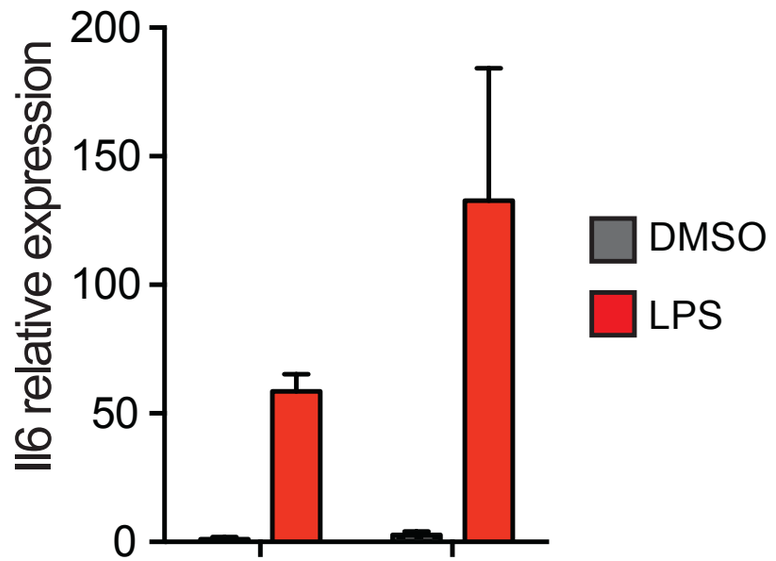


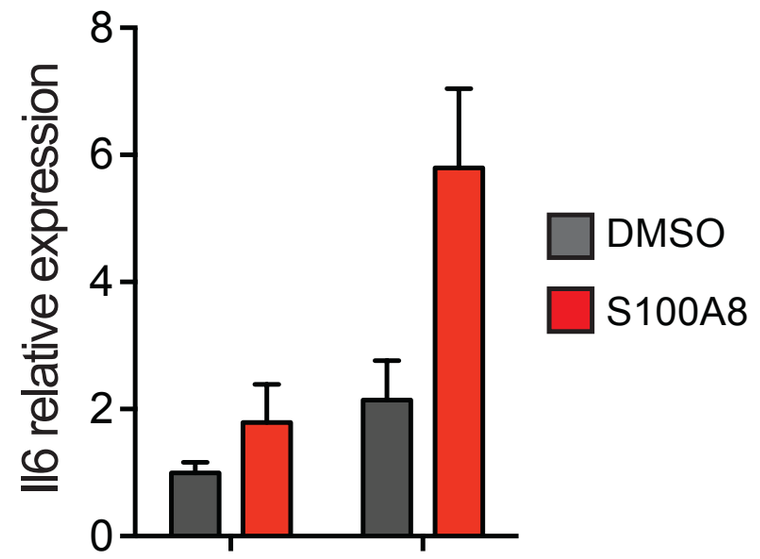


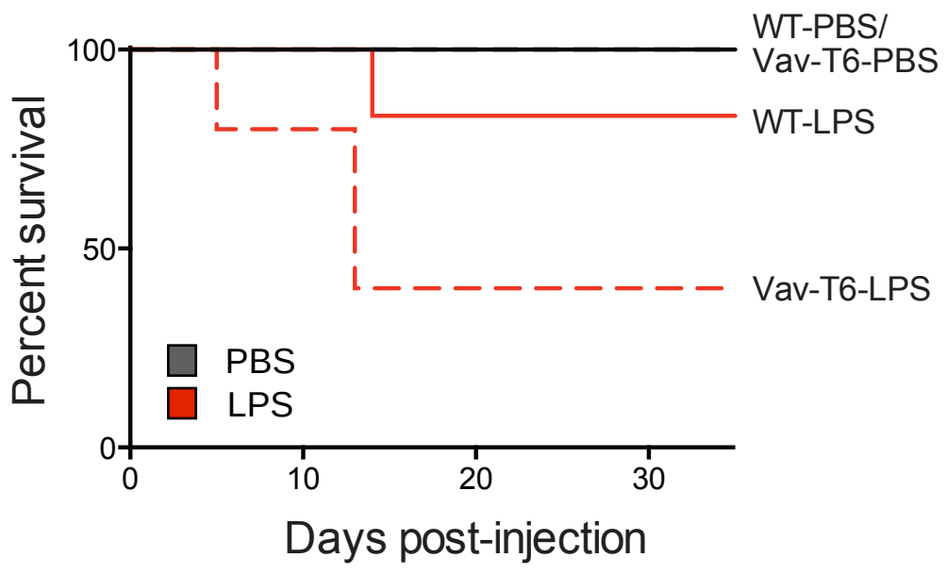
Varney et al., Leukemia (2016)

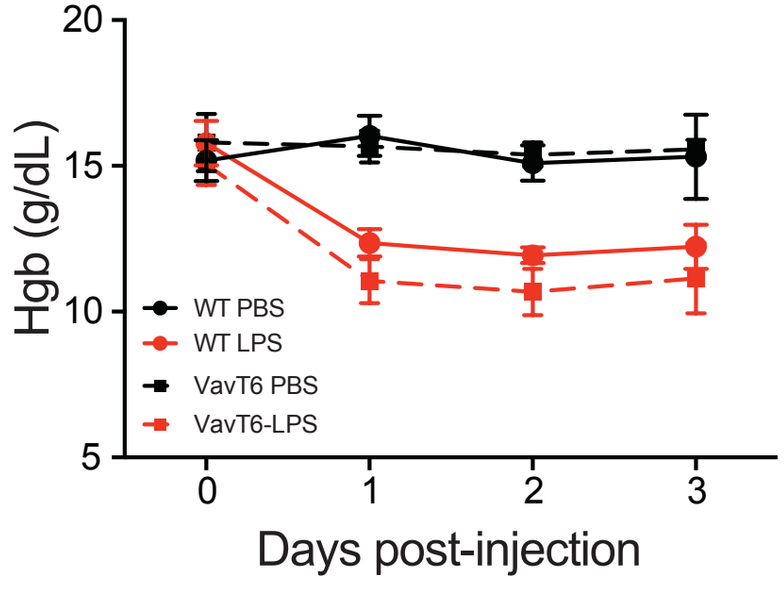
TRAF6 overexpression results in differential sensitivity to TLR agonists











Fang et al., Nature Immunology (in press); Muto et al., unpublished

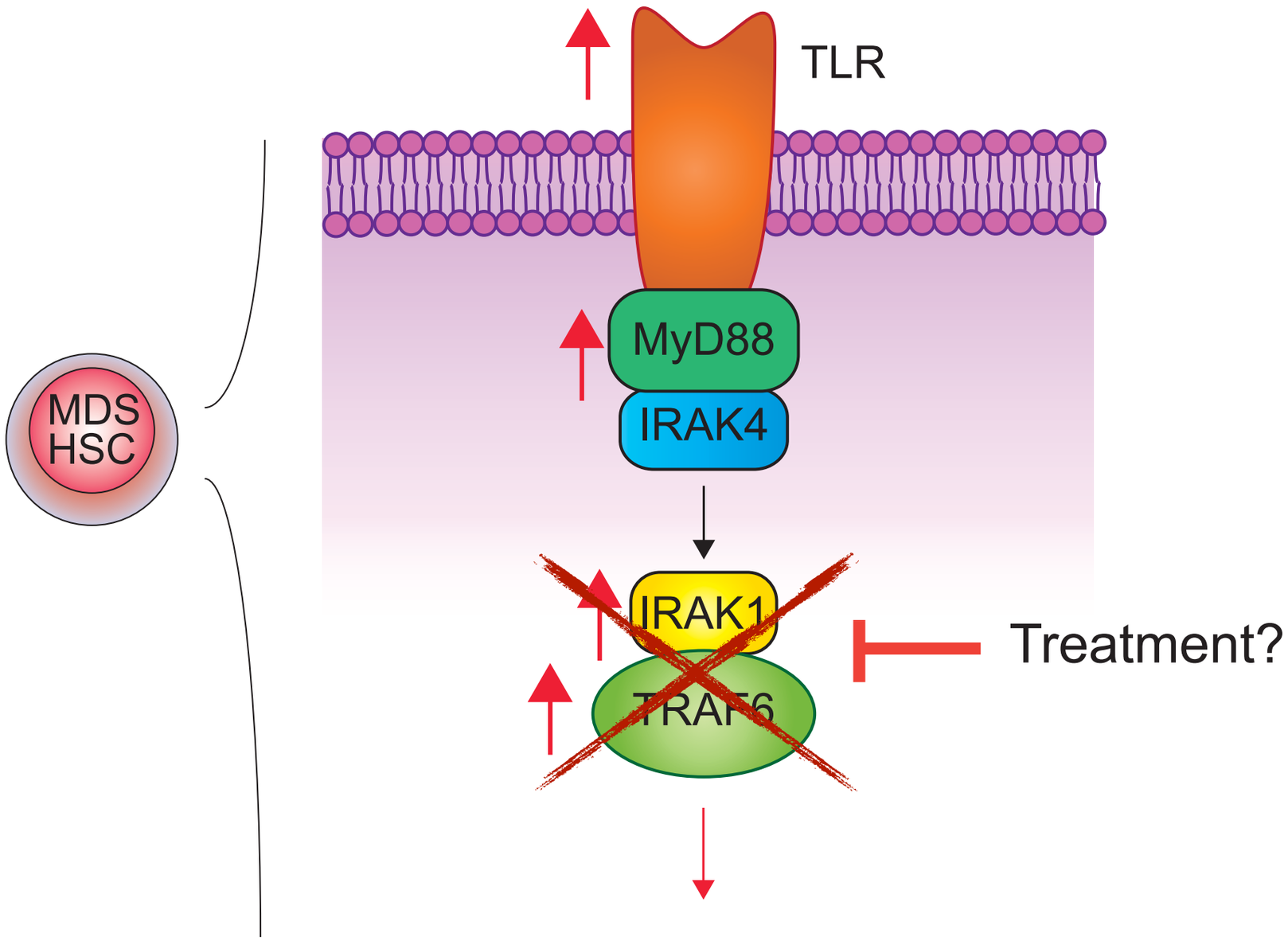
<u>Summary I</u>: Regulation of TLR/TRAF6 by miR-146 and TIFAB, two del(5q) MDS genes

- Cooperating genetic events in del(5q) MDS activate the TLR/TRAF6 pathway.
  - miR-146a = TRAF6 mRNA
  - TIFAB = TRAF6 protein

- Combined deletion of miR-146a and TIFAB synergistically regulates gene networks in HSPC.
  - Interferon, EGFR, immune regulation, and HSC/myeloid differentiation
  - Increased sensitivity to TLR ligands

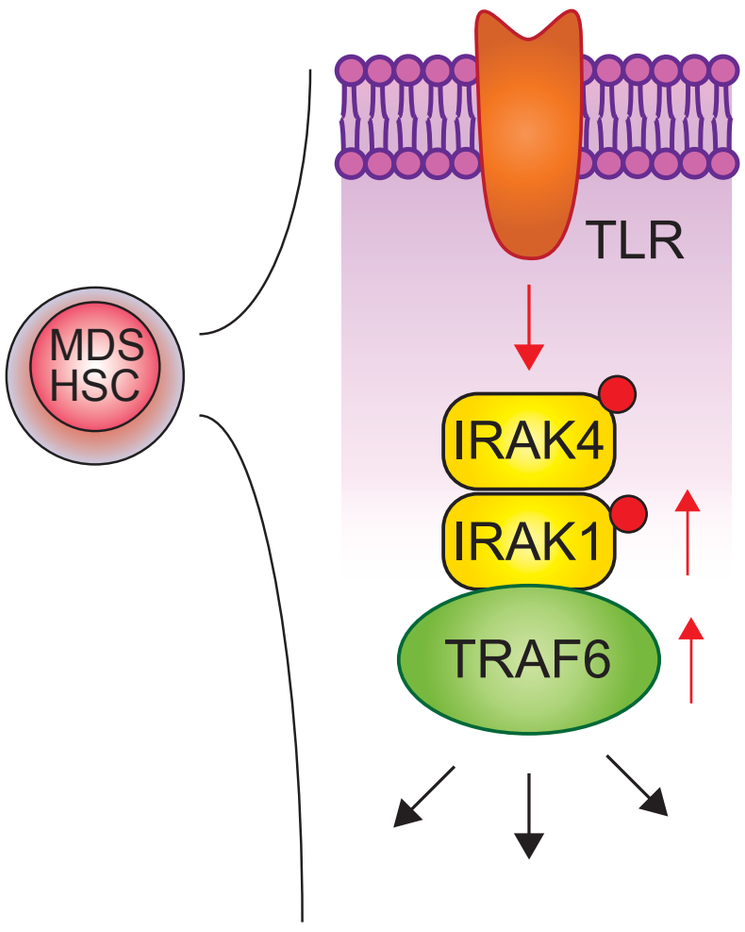
- Combined deletion of miR-146a and TIFAB (**via TRAF6 and IRAK1/4 activation**) impacts HSPC function and severity of hematologic defects.

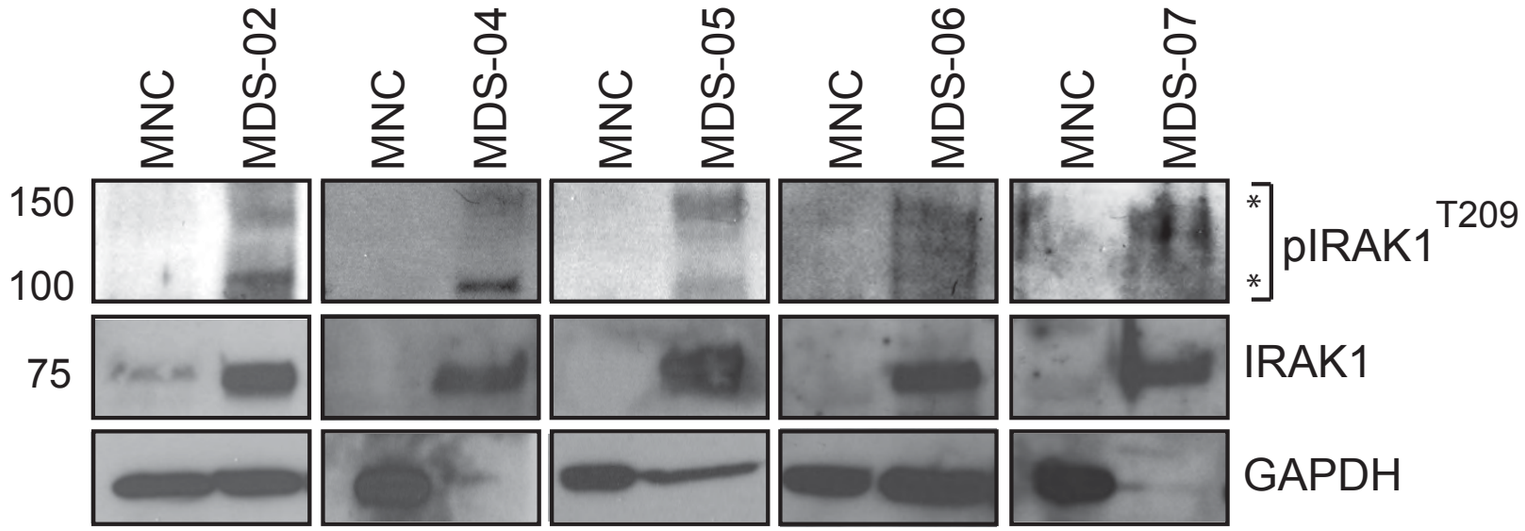
Can the TLR signaling complex be targeted in MDS?

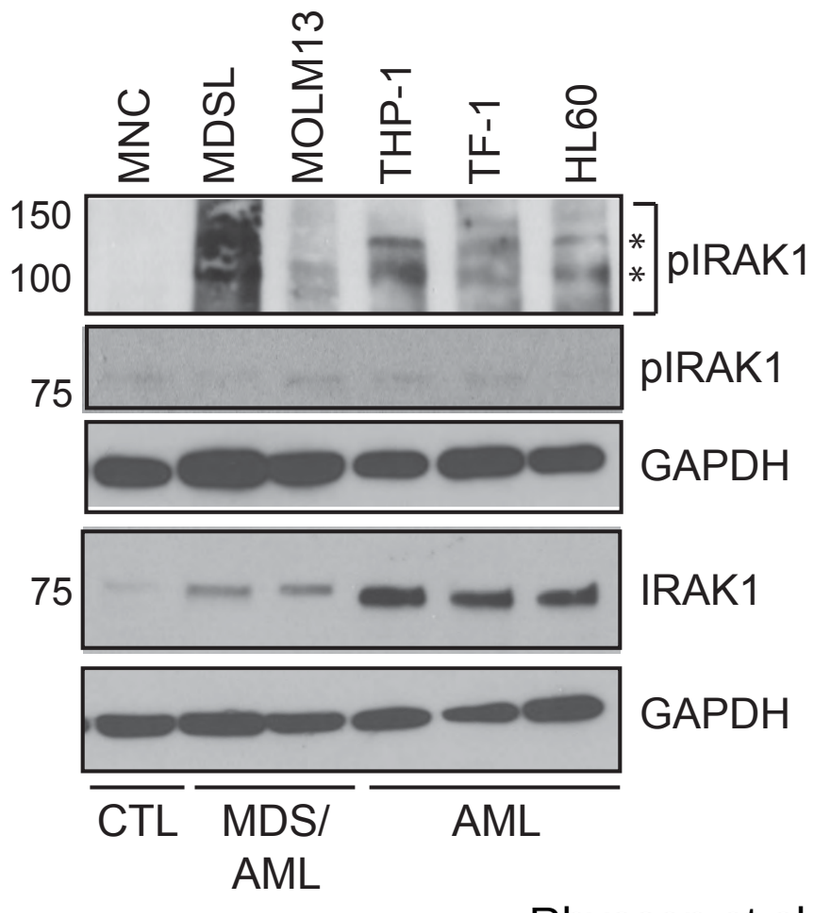


Rhyasen et al., Cancer Cell (2013)

IRAK1 is activated in MDS

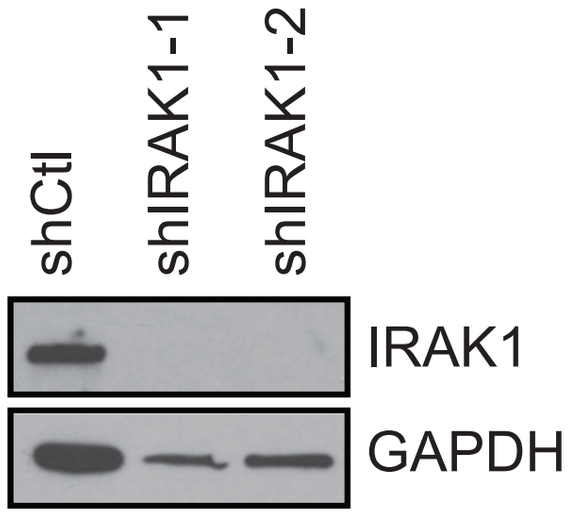


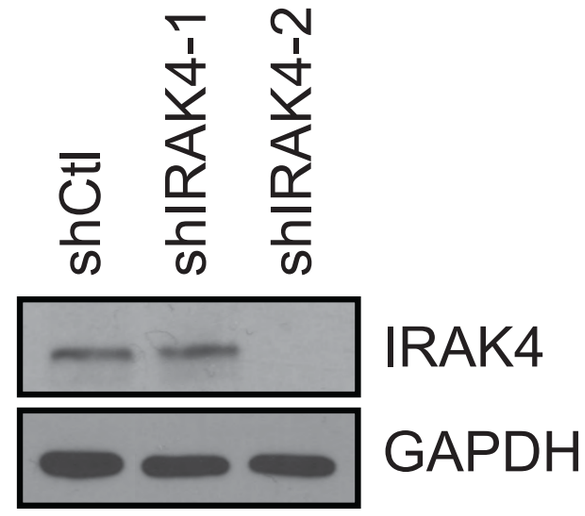


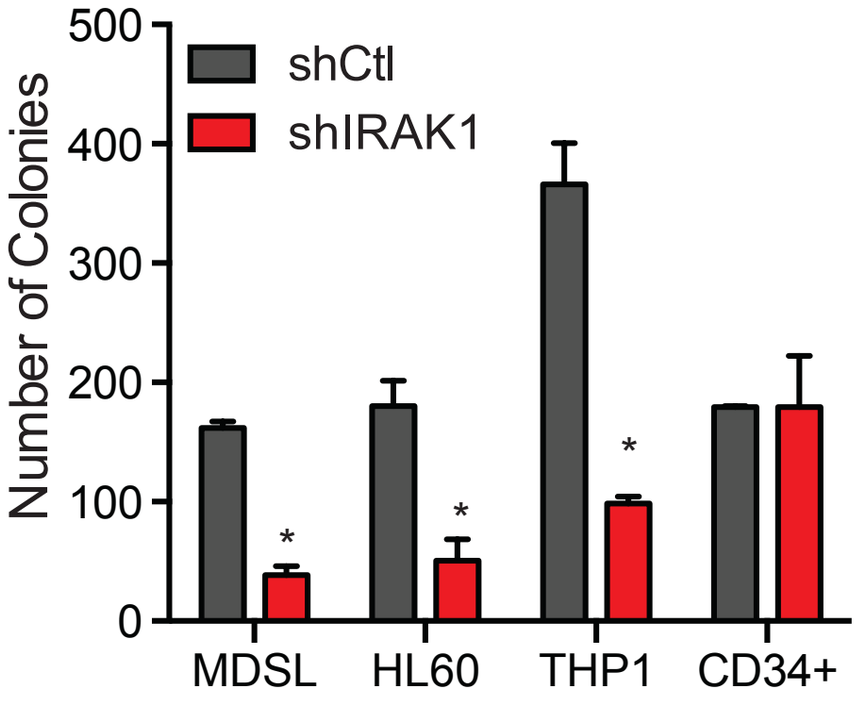


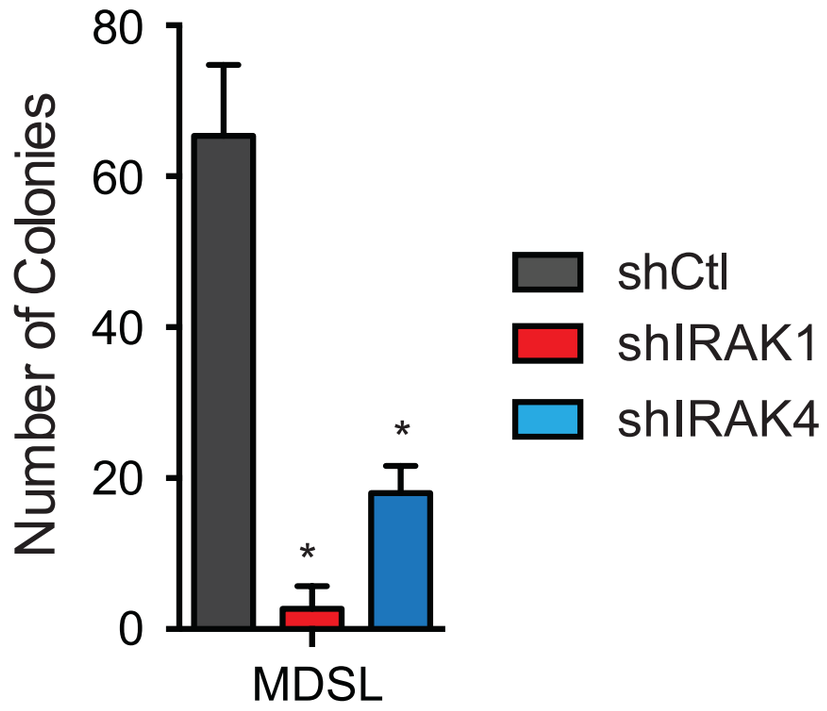
Rhyasen et al., Cancer Cell (2013)

Knockdown of IRAK1 or IRAK4 impairs MDS/AML HSPC function *in vitro*



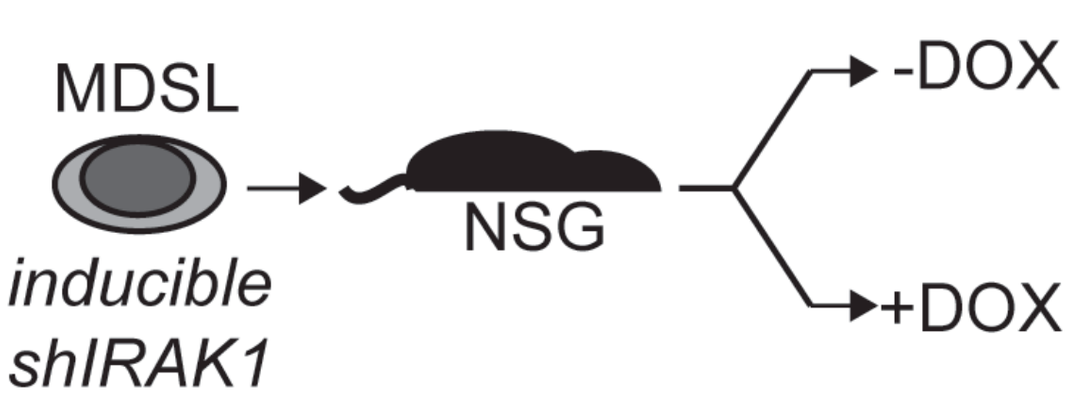


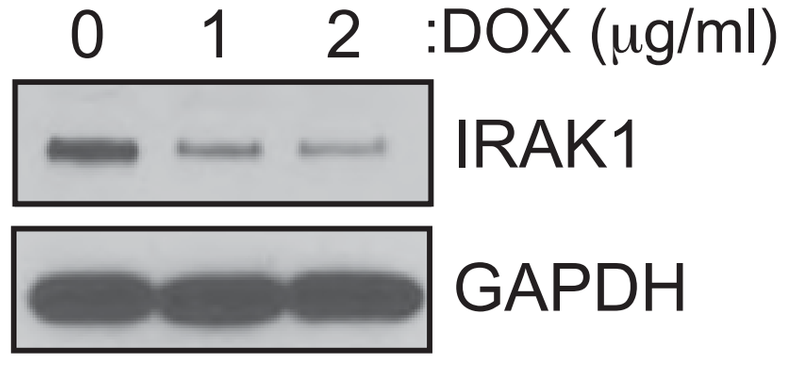


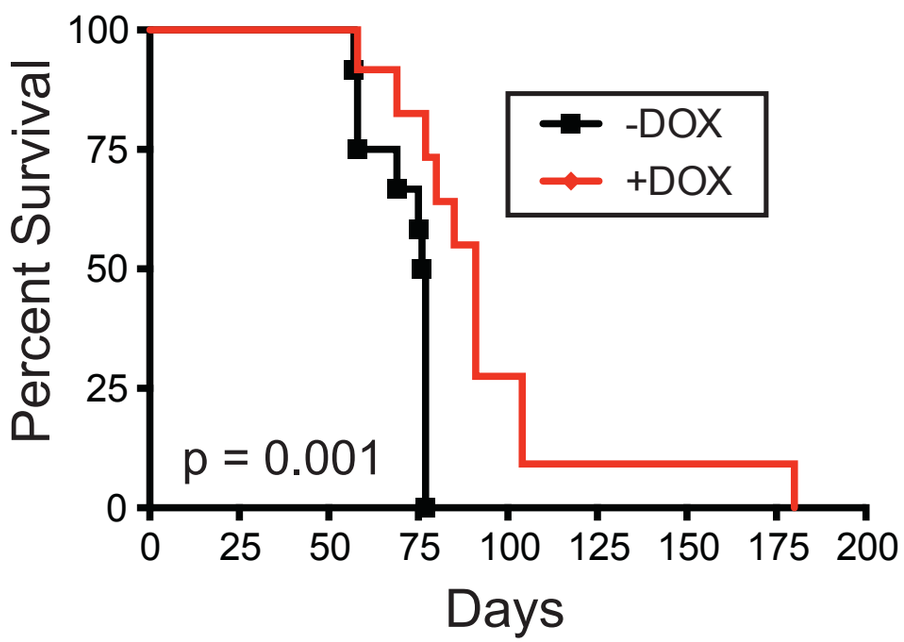


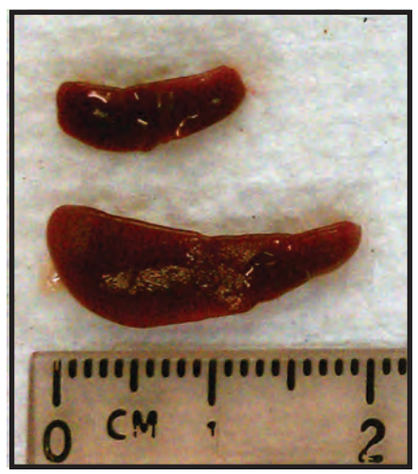
Rhyasen et al., Cancer Cell (2013)
Rhyasen et al., Exp Hem (2014)

Knockdown of IRAK1 impairs MDS HSPC function *in vivo*









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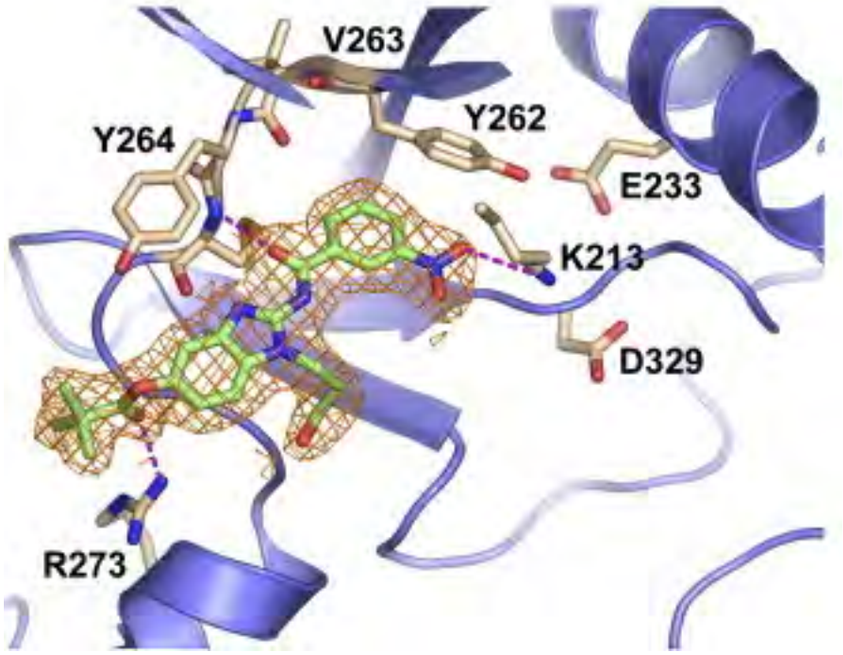
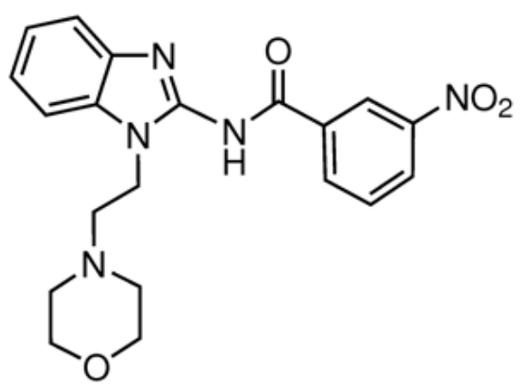
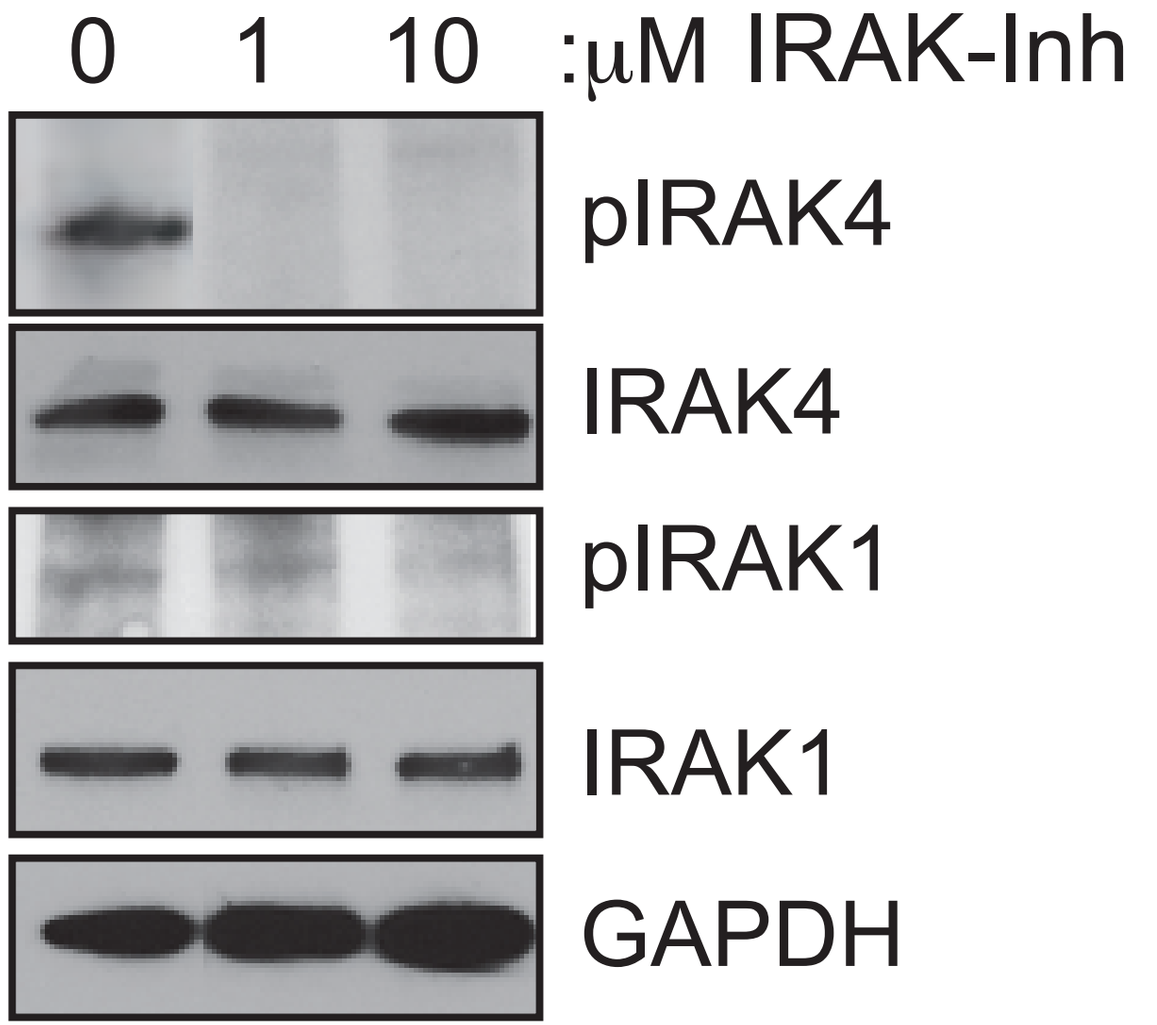
Rhyasen et al., Cancer Cell (2013)

Pharmacological inhibition of IRAK1/4



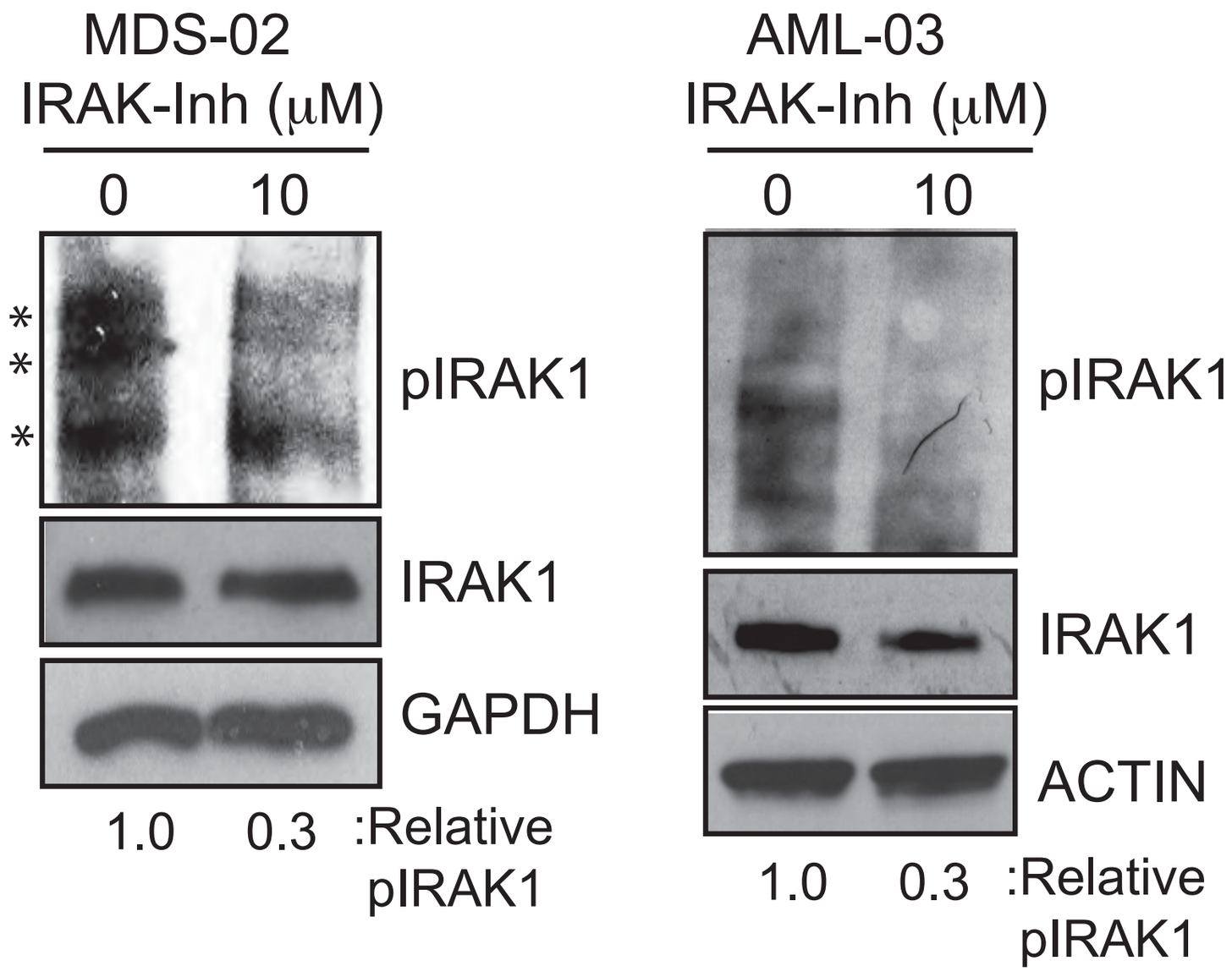


‘IRAK-Inh’
(acyl-2-aminobenzamidazole)



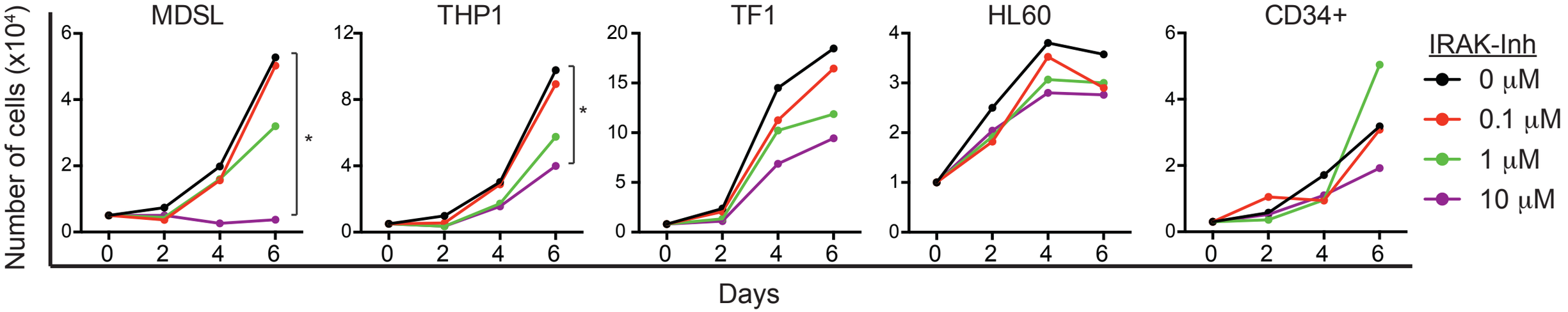
Rhyasen et al., Cancer Cell (2013)

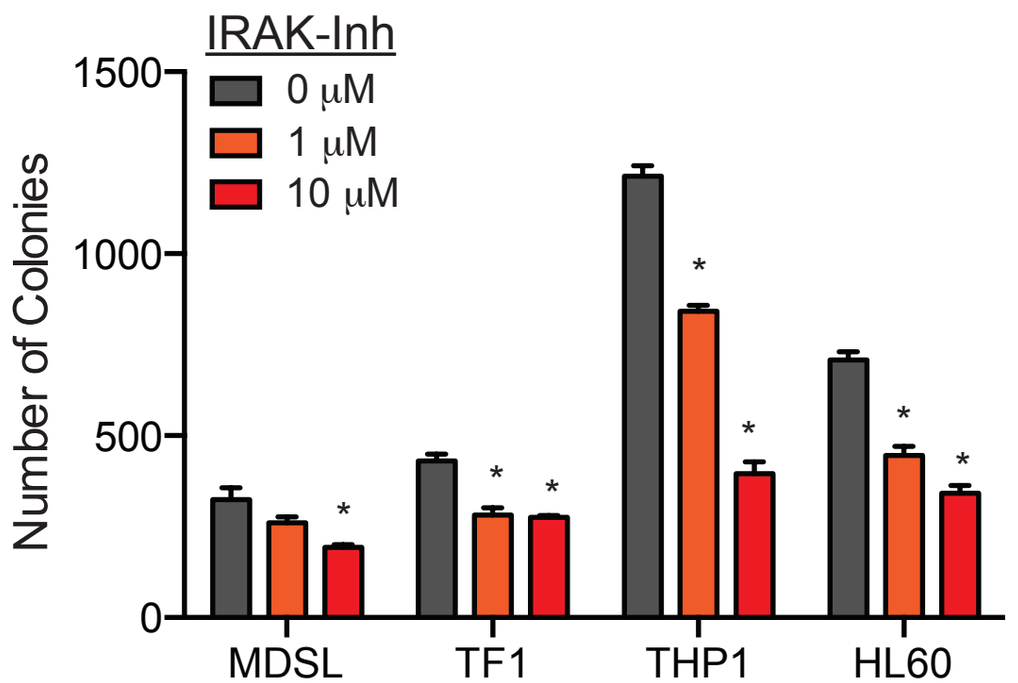
Pharmacological inhibition of IRAK1/4 in primary MDS/AML



Rhyasen et al., Cancer Cell (2013)

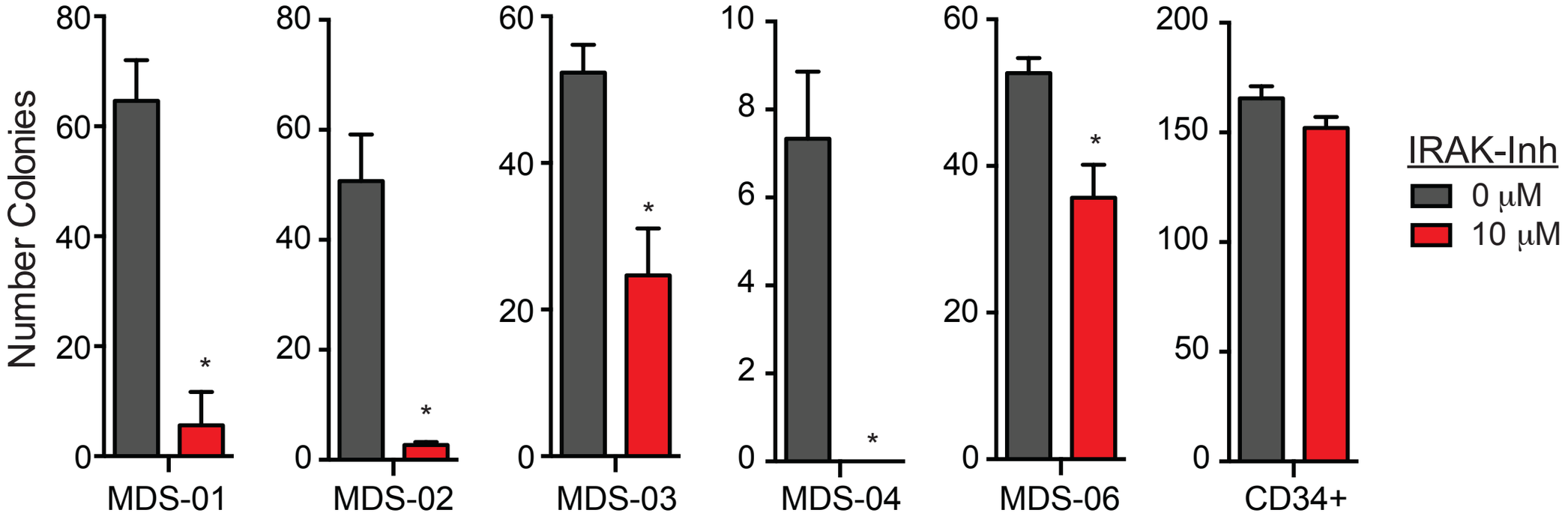
IRAK-Inh suppresses MDS/AML cell lines *in vitro*





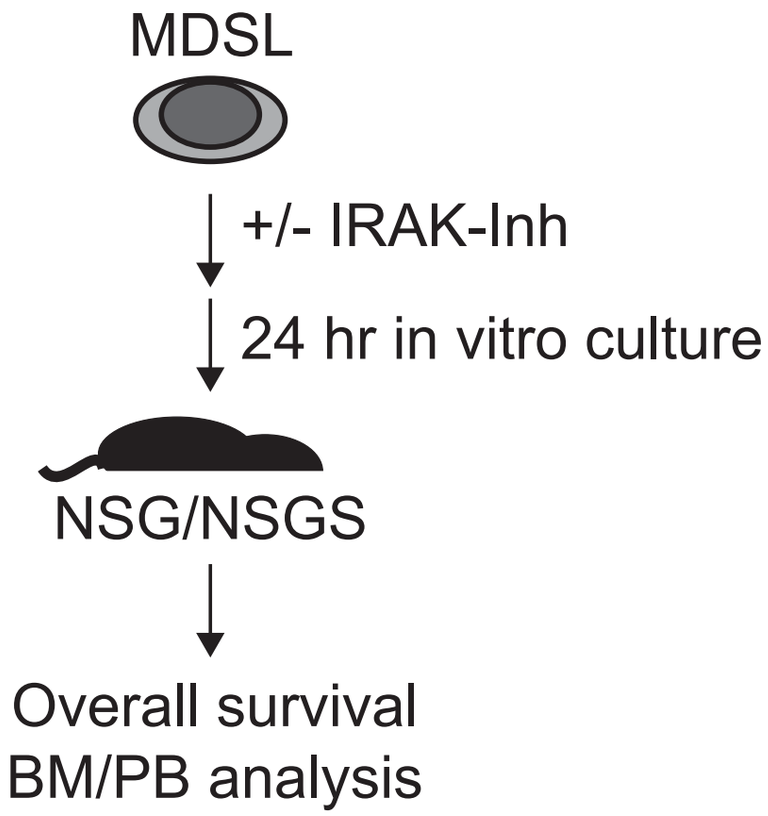
Rhyasen et al., Cancer Cell (2013)

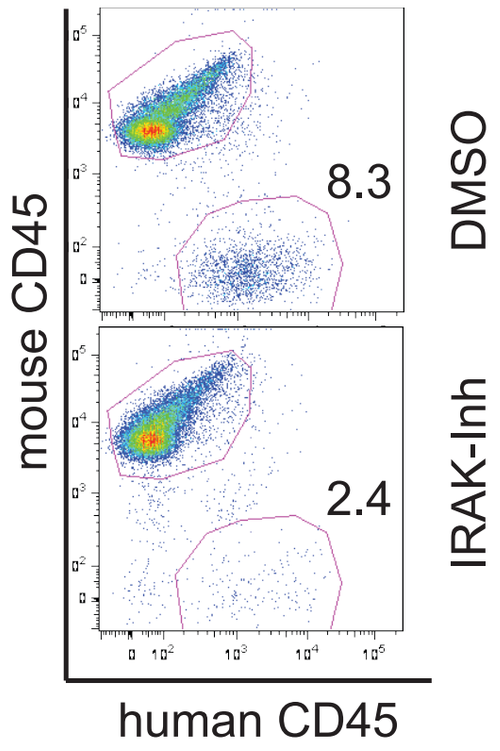
IRAK-Inh is effective at targeting primary MDS cells, but spares normal BM HSPC

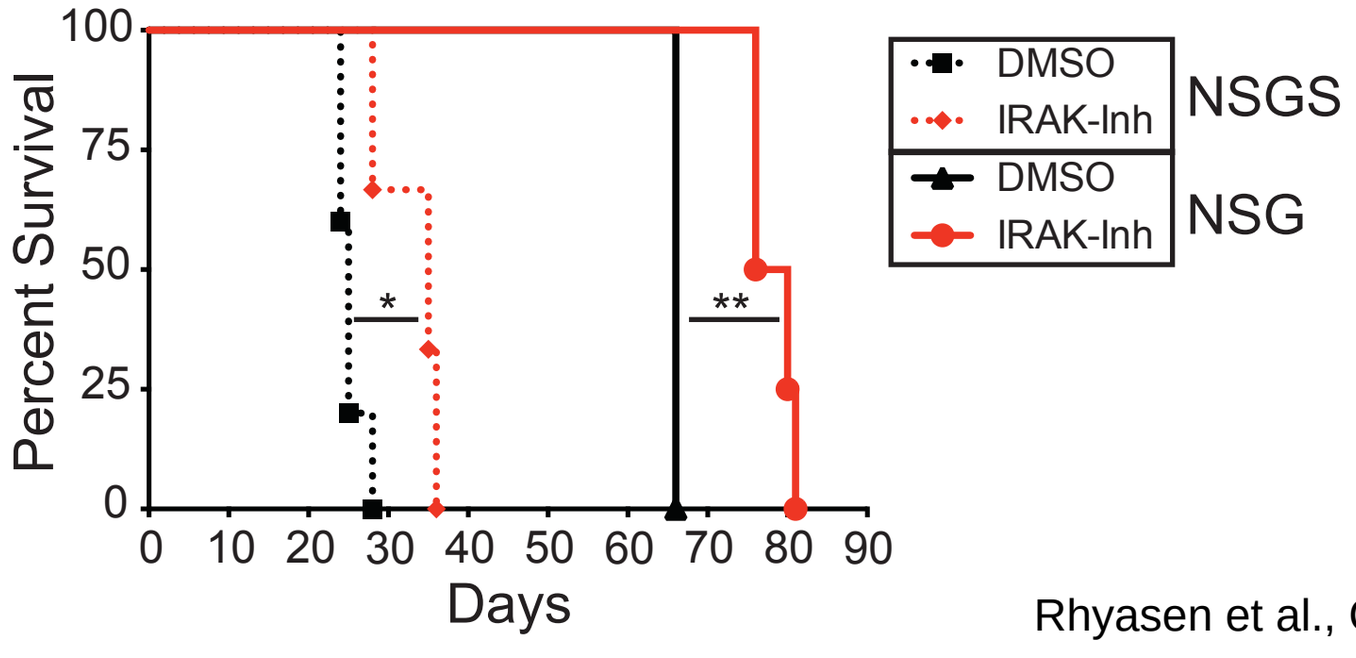


Rhyasen et al., Cancer Cell (2013)

Pre-treatment of MDSL cells with IRAK-Inh suppresses disease *in vivo*

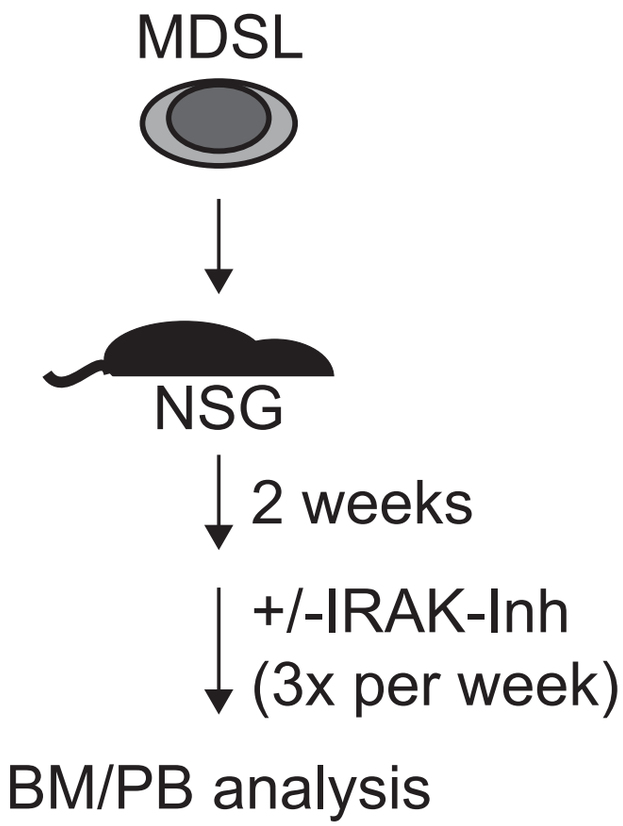


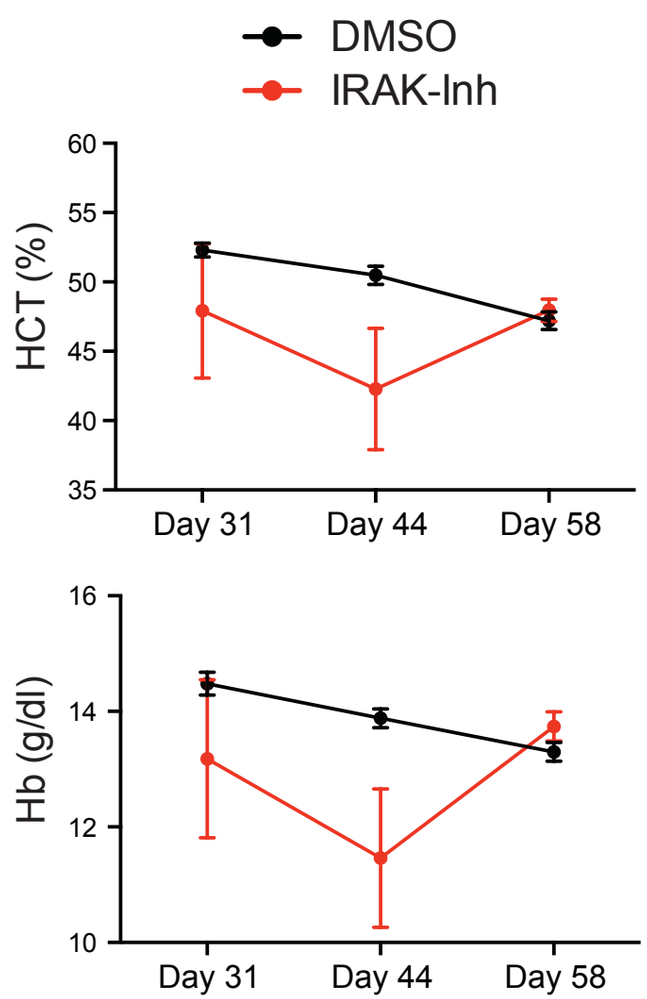


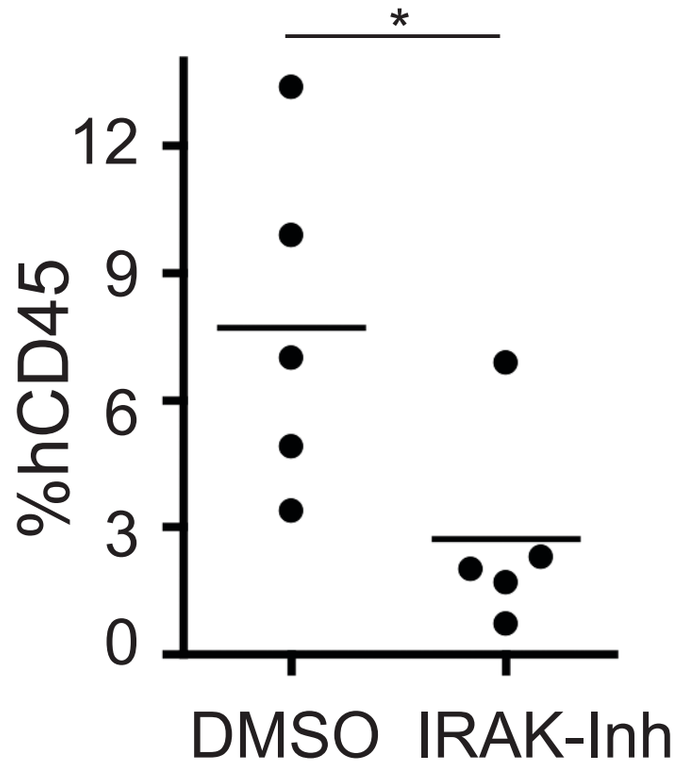


Rhyasen et al., Cancer Cell (2013)

In vivo IRAK-Inh treatment improves anemia and diminishes MDSL engraftment







Rhyasen et al., Cancer Cell (2013)

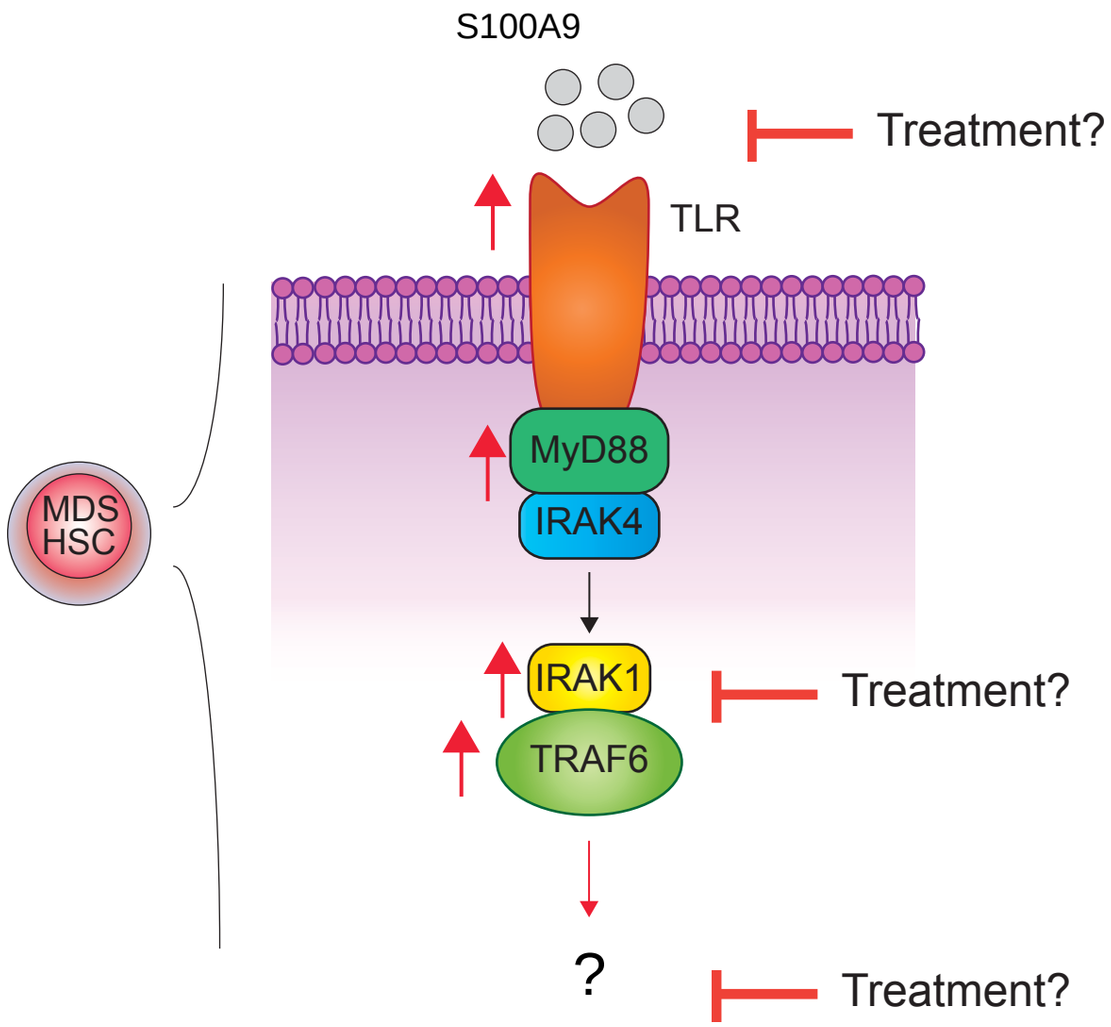
Summary II: IRAK1/4 as a target for MDS and AML

- IRAK1 and IRAK4 is hyperactivated and required for maintaining the leukemic state of MDS and AML cells via TRAF6 signaling.

- IRAK-Inh targets MDS-propagating cells:
  - *increased apoptosis*
  - *reduced progenitor function*
  - *no effect on normal CD34+ cells*
  - *not sufficient to target AML-propagating cells*

- Dire need of compounds targeting IRAK1/4 with drug-like properties and clinical potential.

Alternative and emerging immune-related targeting approaches for MDS



1. S100A9 chimeric decoy receptor (CD33-IgG1)
2. TLR2 neutralization IgG4
3. IRAK1/4 inhibitors
4. Downstream effectors (p38 inhibitors)

JCI The Journal of Clinical Investigation

Induction of myelodysplasia by myeloid-derived suppressor cells

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blood

The NLRP3 Inflammasome functions as a driver of the myelodysplastic syndrome phenotype

Ashley A. Basiorka,[1] Kathy L. McGraw,[2] Erika A. Eksioglu,[3] Xianghong Chen,[3] Joseph Johnson,[4] Ling Zhang,[5] Qing Zhang,[2] Brittany A. Irvine,[2] Thomas Cluzeau,[6-8] David A. Sallman,[2] Eric Padron,[2] Rami Komrokji,[2] Lubomir Sokol,[2] Rebecca C. Coll,[9] Avril A. B. Robertson,[9] Matthew A. Cooper,[9] John L. Cleveland,[10] Luke A. O'Neill,[11] Sheng Wei[3] and Alan F. List[2]

nature medicine

Rps14 haploinsufficiency causes a block in erythroid differentiation mediated by S100A8 and S100A9

Rebekka K Schneider[1,2], Monica Schenone[3], Monica Ventura Ferreira[2], Rafael Kramann[4], Cailin E Joyce[5], Christina Hartigan[3], Fabian Beier[2], Tim H Brümmendorf[2], Ulrich Germing[6], Uwe Platzbecker[7], Guntram Büsche[8], Ruth Knüchel[9], Michelle C Chen[1], Christopher S Waters[1], Edwin Chen[1], Lisa P Chu[1], Carl D Novina[5], R Coleman Lindsley[1,5], Steven A Carr[2] & Benjamin L Ebert[1,3]

Leukemia

Toll-like receptor alterations in myelodysplastic syndrome

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Clinical Cancer Research

A Phase I Study of Oral ARRY-614, a p38 MAPK/Tie2 Dual Inhibitor, in Patients with Low or Intermediate-1 Risk Myelodysplastic Syndromes

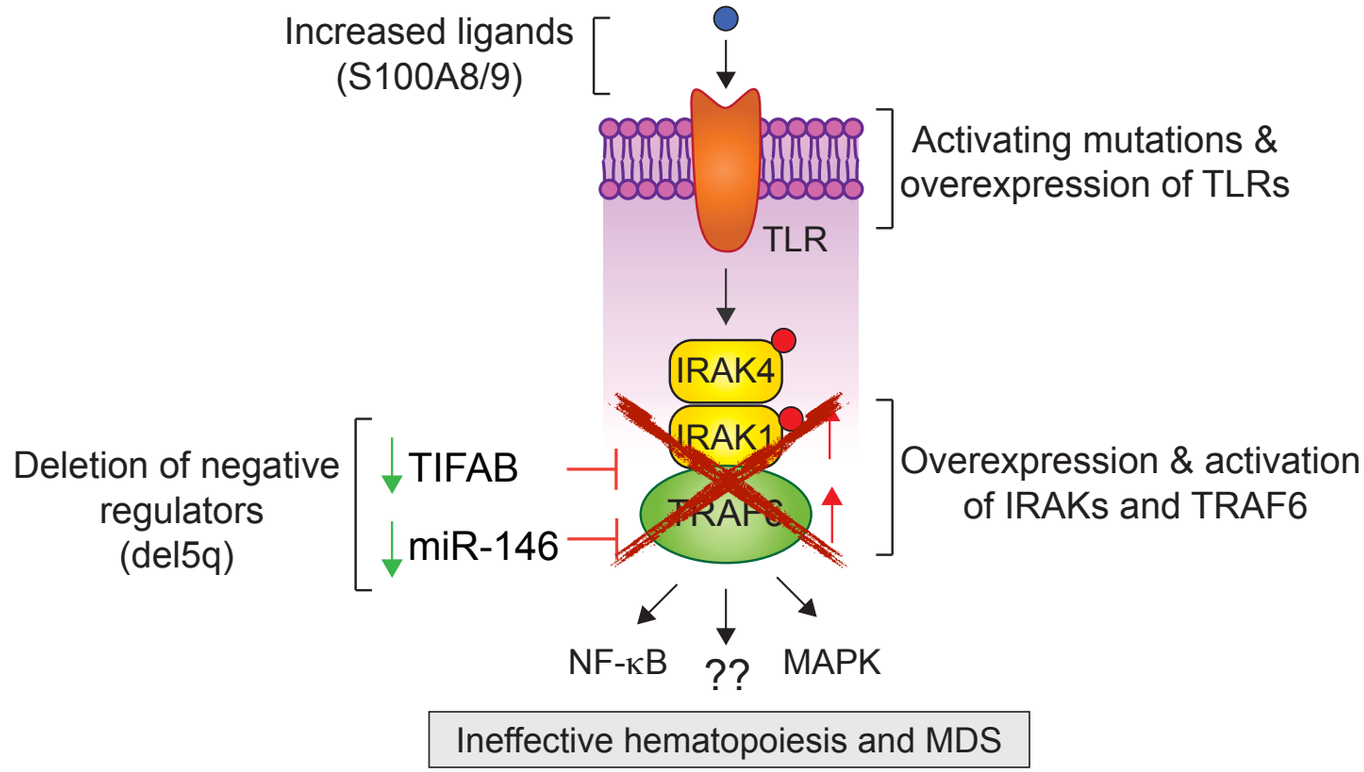
Guillermo Garcia-Manero[1], Hanna J. Khoury[2], Elias Jabbour[1], Jeffrey Lancet[3], Shannon L. Winski[4], LouAnn Cable[4], Selena Rush[4], Lara Maloney[4], Grant Hogeland[4], Mieke Ptaszynski[4], Monica Cabrero Calvo[1], Zach Bohannan[1], Alan List[3], Hagop Kantarjian[1], and Rami Komrokji[3]

blood

Inhibition of overactivated p38 MAPK can restore hematopoiesis in myelodysplastic syndrome progenitors

Tony A. Navas, Mani Mohindru, Myka Estes, Jing Ying Ma, Lubomir Sokol, Perry Pahanish, Simrit Parmar, Edwin Haghnazari, Li Zhou, Robert Collins, Irene Kerr, Aaron N. Nguyen, Yin Xu, Leonidas C. Platanias, Alan A. List, Linda S. Higgins, and Amit Verma

<u>Conclusions:</u> Chronic innate immune signaling is an important mechanism and druggable target in MDS



- Chronic immune signaling contributes to cell-intrinsic and systemic hematopoietic defects that contribute to the pathogenesis of MDS.

- Combined deletion of TIFAB and miR-146a, two del(5q) MDS genes, enhance TRAF6 signaling and contribute to hematopoietic defects.

- TRAF6 overexpression is sufficient to induce hematopoietic defects and features of MDS.

- Targeting the TLR/IRAK/TRAF6 signalosome may be an effective therapeutic strategy against MDS-propagating cells.

Final Remark

<u>TLR/TRAF6 induced MDS/AML is a two-step process:</u>

- one step provides the normal cell with the new ability to activate TLR/TRAF6 as a consequence of aberrant epigenetic regulation or deletion of negative regulators;

- the second step involves progression to a malignant state through the constitutive activation of oncogenic pathways mediated by TLR/TRAF6 signaling.

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