Aging and Hematopoiesis

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Disclosures

- Nothing to disclose
MDS is an Age-Associated Disease

MDS incidence in different age groups in the United States (2001 to 2008). (Adapted from NCI SEER*Stat Database.)
Stem Cell Theory of Aging

Liu and Rando 2011  JCB vol. 193 no. 2 257-266
### Hematopoiesis Changes with Age

<table>
<thead>
<tr>
<th>HSC</th>
<th>Progenitors</th>
<th>Effector Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mouse</strong> Lineage IL7α c-Kit Sca1+</td>
<td><strong>Human</strong> Lineage CD90+ CD45RA- CD34+ CD38+</td>
<td><strong>Erythrocytes</strong> Anemia <strong>Platelets</strong> Platelet activation, and thrombosis <strong>T-cells</strong> T and B cell numbers and function <strong>B-cells</strong> <strong>NK cells</strong> NK numbers Activity? <strong>Dendritic cells</strong> Altered function? <strong>Macrophages</strong> Function <strong>Neutrophils</strong> Alterations in receptors and signaling <strong>Granulocyte-macrophage progenitor (GMP) frequency</strong> <strong>Basophils</strong> Altered function? <strong>Eosinophils</strong> Function <strong>Mesenchymal cells</strong> Altered activation? <strong>Osteoclasts</strong> Osteoclast activity</td>
</tr>
</tbody>
</table>

- Increased HSC number ✔
- Decreased HSC long-term reconstitution potential ✔
- Myeloid Biased Differentiation ✔
- Decreased lymphocyte function/production ✔
- Decreased red cells ✔
- Clonal Expansion ✔
- Risk of MDS/AML ✔

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And many, many more……

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Gazit et al. 2008 Seminars in Hematology
Age-Related HSPC Changes Occur Gradually

Fold Change in Frequency

**HSC (LSK CD150+34-)**

- **9-11wk**
- **12m**
- **27m**

**Safak Yalcin**
Age-Related Changes Occur Gradually in Human HSCs

Pang, et al., PNAS, 2013
Mechanisms of HSC Aging

Signaling Pathways Involved in Stem Cell Aging

Regulators of stem cell aging

- ATM
- PTEN
- AKT
- mTOR
- AMPK
- SIRT1
- SIRT3
- SIRT6
- Atg7
- FoxO3
- FoxO4
- IGF-1
- FGF2
- p16^{INK4a}
- TGFβ
- NF-κB

Mitochondrial function

- PGC-1α
- PGC-1β

Autophagy

Proteasome activity

Cell cycle regulation

Stem cell quiescence

Stem cell senescence

Genomic stability

Stem cell survival

Nutrient sensing/uptake

Protein quality control

Systemic inflammation

• The aging hematopoietic system undergoes many changes.
• Many of the changes observed in the hematopoietic system with age are due to alterations in HSCs and committed progenitors.
• Age-related hematopoietic changes occur gradually over time, but can potentially be reversed.
The MDS Disease-Initiating Cell is the HSC


Nilsson et al., Blood, 2000
Nilsson et al., Blood, 2002
Tehranchi et al. NEJM 2010
Will et al., Blood 2012
Pang et al., PNAS, 2013
Meydouf et al, Cell Stem Cell, 2014
Woll et al., Cancer Cell, 2014

Pang et al., PNAS 2011
## Similarities Between MDS HSCs and Old HSCs

<table>
<thead>
<tr>
<th>Feature</th>
<th>Age</th>
<th>MDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased HSC number</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Decreased HSC long-term reconstitution potential</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Myeloid Differentiation Bias</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Decreased lymphoid production</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Decreased red cell production</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Clonal Expansion</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Risk of MDS/AML</td>
<td>✔</td>
<td>✔</td>
</tr>
</tbody>
</table>
Clonal Hematopoiesis in Aging

Xie et al, Nat Med, 2014

Jaiswal, et al., NEJM, 2014
Clonal Hematopoiesis of Indeterminate Potential (CHIP) – Precursor State for Myeloid Malignancies

Steensma et al. Blood 2015;126:9-16
Summary (2)

• The HSC is the disease-initiating cell in MDS
• MDS and hematopoiesis in the elderly exhibit similar features.
• Clonal hematopoiesis in normal elderly characterized by the acquisition of mutations thought to be drivers of MDS pathogenesis; however, *not all aging is associated with somatic mutations.*
• Clonal hematopoiesis is a risk factor for MDS/AML as well as increased risk of mortality from non-hematopoietic causes.

*Question: Are aged HSCs and MDS HSCs the same?*
Numerous Transcripts are Dysregulated in MDS HSCs Compared to Age-Matched Control HSCs

McGowan et al., Blood 2011
Ribosomal Protein Transcript Deficiencies Characterize MDS HSC

McGowan et al., Blood 2011

HSC

CD34+

21 Rp’s

38 Rp’s

Sridhar K et al. Blood 2009;114:4847-4858
### Table 3. Gene pathways aberrantly methylated in MDS HSCs

<table>
<thead>
<tr>
<th>Hypomethylated in MDS HSCs</th>
<th>Biologic functions</th>
<th>Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1</strong></td>
<td>Gene expression, cellular movement, embryonic development</td>
<td>AKT1S1, CDC16, CDC25B, CDK3, CHAF1B, DTX1, EIF4EBP1, ERBB3, FGFR1, FZ1R1, GALNT14, GATA4, GRLF1, GRWD1, ITM2C, MUC4, MUC5AC, NOTCH1, PARD3, RPS6KA4, TBX5, TFDP1, TFF1, TP53BP2, TRIM24, WDR5</td>
</tr>
<tr>
<td><strong>2</strong></td>
<td>Carbohydrate metabolism, lipid metabolism, small-molecule biochemistry</td>
<td>AGRN, CAPN5, CASD1, COL6A2, DDX1, ENG, HIP1, HIP1R, LAMA1, LCAT, LIMS1, MAGE1A (includes EG4100), M3AT3, MIA, NANOQ, NF2, P4HA3, PDLIM2, PXN, RPL22, SGS3M3, SH3GL2, SLC12A6, TGM2, TSPYL2</td>
</tr>
<tr>
<td><strong>3</strong></td>
<td>Dermatologic diseases and conditions, genetic disorder, skeletal and muscular system Development and function</td>
<td>CSDD2, CTBP1, EDARADD, HDAC4, KCNC1, KDHRBS2, LTB, MAP3K14, MEOX1, MYOG, NLRC4, OTUB2, PGLYRP1, PKP1, SMYD2, SNRPD3, SRL, STAT5A, SYNC, TARD8P, TNFRSF4, TNPO2, WIZ</td>
</tr>
<tr>
<td><strong>4</strong></td>
<td>Cardiovascular system Development and function, embryonic development, organismal development</td>
<td>CBLC, CYP17A1, CYTH2, DRD5, FZD5, GNG3, GPR35, GPR162, GPR179, IL28, LPAR1, LTBR42, Mapk, MTHR1A, NCKAP1, NRIP1, PLXNA1, PTGDR, PTGER3, RNASE2, SLC12A2, SLC16A3, SLC7A1, SLC9A1</td>
</tr>
<tr>
<td><strong>5</strong></td>
<td>Cellular movement, respiratory disease, hematologic system development and Function</td>
<td>ANGPT2, CXADR, DNAH1, DUSP1, EPK1, F7, GNAZ, IFITM1, LTA, MAP3K1, MBP, MIFGE8, MICAL2, PIGR, PLA2G7, PON2, PRKCH, PTMA, SLC6A4, TACSTD2, TICAM1</td>
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<tr>
<td><strong>1</strong></td>
<td>Cancer, reproductive system disease, cardiovascular disease</td>
<td>BAG2, CDC16, CITED1, CLASP1, ECEL1, EREG, GANAB, GGT1, GPA1A, KIDINS220, MAN3C1, MAPRE3, MRP4, MCM4, MB, P4HA2, PFDN6, PHKA2, PIGK, PPAP2B, SIAH2, SPG20, SPRY2, SRDS6A2, TP53T1, TRIP10, TUBA1A, TUBA1C, TUBB, TYROBP</td>
</tr>
<tr>
<td><strong>2</strong></td>
<td>Lipid metabolism, small-molecule biochemistry, gastrointestinal disease</td>
<td>B4GALT1, CHRNA1, CILP, CLP2, DLL3, DOK6, EWSR1, GLS, GP1BB, GSP1T1, HIVEP1, LAO1, MEOX2, MSX2, MUC1, NDUF1B, NOTCH4, OLFM2, PGLS, PTD3C, RET, SIX3, ST13, STAG2, SYT1, TNF, ZDHHC3</td>
</tr>
<tr>
<td><strong>3</strong></td>
<td>Molecular transport, protein trafficking, behavior</td>
<td>ARL4A, CAMK2A, CDC106, CDKN1B, CRX, DKK1, DLK1, EFEMP1, HOX7A, KAT7A, MB01, MLL, MYC1C, NELF, NUTF2, PRKD2, PTC2D2, RAN, RFC1, RPL12 (includes EG8136), RPS8, SETDB1, SETMAR, TBL1X, TNPO2, UHRF1, WDR46</td>
</tr>
<tr>
<td><strong>4</strong></td>
<td>Gene expression, tissue morphology, nervous system development and function</td>
<td>ALDH1B1, APOE, CBR3, CHSY1, FAM129B, FCUA1, GDPD5, GNA12, HLTF, IGFBP6, LRRRC8A, MTHR6, PHOX2A, PPM1B, PRDX1, RH10, SP1, SP2, STAT6, STOM, UBE2D, USP3, USP4, USP4A, ZCCHC4</td>
</tr>
<tr>
<td><strong>5</strong></td>
<td>Cell cycle, cellular growth and proliferation, genetic disorder</td>
<td>ADC, ADRM1, CDKN1A, EF4F1, EIF6, EIF3J, EIF4B, HIST1H3E (includes EG3012), KIF20A, LYN, NMT1, N2E21 (includes EG7101), NUDT5, PHC1, PSM4A, PSM4B, PSM4C, PSM5C, SNCAIP, TGFBI11, TMEM126B, TNNT1, TRIM41, UBE2I</td>
</tr>
</tbody>
</table>
MDS HSCs are Genetically Heterogeneous

Papaemmanuil E et al., Blood, 2013
Pang et al, PNAS 2013
Tehranchi R et al. NEJM 2010;363:1025-1037

A

Healthy Subject
CD38

10^0 10^1 10^2 10^3 10^4

2.14% 0.30%

CD34

CD90

Patient 6 (before treatment)
CD38

10^0 10^1 10^2 10^3 10^4

1.43% 0.55%

CD34

CD90

253/253 del(5q)

Patient 6 (during treatment)
CD38

10^0 10^1 10^2 10^3 10^4

0.41% 0.08%

CD34

CD90

114/250 del(5q)

Stem Cells

0/250 del(5q)

Progenitor Cells

0/250 del(5q)

250/250 del(5q)

114/250 del(5q)

0/155 del(5q)
scRNA-seq Reveals that MDS and Aged HSCs are Different, But Heterogeneous
Despite Vast Intratumoral Heterogeneity, Cells Cluster With Other Cells From the Same Patient

Single Cell RNA-seq of HSCs from Six MDS Patients (Pre- and No Treatment Samples)

union of genes in top 10% of loadings on PC2, PC3, PC4
Pre-Therapy MDS HSC Transcriptomes May Predict Decitabine Responses

Responders and Non-responders are Separated by PC3
HSCs From Responders (R) Are More Similar to Normal HSCs than HSCs from Non-responders or Untreated Cases (PC2)
Summary (3)

• MDS HSCs are distinct from aged HSCs
  – Unique gene expression profile
  – Unique methylome
  – Unique protein surfaceome

• MDS HSCs exhibit heterogeneity
  – Genetic heterogeneity
  – Transcriptional heterogeneity

• MDS HSCs exhibit gene signatures
  – May predict responses to hypomethylating agents
  – Reflect a global reduction in ribosomal protein mRNA
Questions:
- How will we define aging? Can we develop a molecular definition of aging? Telomere length, epigenetic changes, etc.?
- Can we delineate the contribution of aging to MDS?
• Constitutive MDS Model (work in progress)
  – No differences in hematopoietic output when MDS BM cells transplanted into normal recipient (young vs. old recipient?)
  – Age-related cell-extrinsic factors modify disease phenotype (induced)
• Induced MDS Model (work in progress)
  – Age is an independent modifier of MDS severity/progression
Rejuvenation Therapy for MDS?

HSC Rejuvenation?
- mTOR inhibition/Rapamycin (Chen et al., Science, 2009)
- Cdc42 Inhibition/casin (Florian et al., Cell Stem Cell, 2011)
- Reprogramming/iPSC (Wahlestedt et al, Blood, 2013)
- Fasting (Cheng et al., Cell Stem Cell, 2014)

Others...

Finkel et al., Nature 2007
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