Genetic complexity

Haferlach et al, *Leukemia* 2014
Serial acquisition of mutations / clonal progression

Walter et al., *NEJM* 2012
Clonal hematopoiesis

Prevalence of Mutation by Age

- Exome sequencing data from peripheral blood of >17,000 individuals
- Unselected for hematologic phenotype

Jaiswal et al., *NEJM* 2014
$DNMT3A$ is frequently mutated
Most subjects had only one mutation

Number of mutations:
- 688 with 1 mutation
- 49 with 2 mutations
- 2 with 3 mutations
- 2 with 4 mutations
Clonal hematopoiesis of indeterminate potential (CHIP)
Clonal hematopoiesis increases the risk of hematologic malignancy

p<0.001
Clonal hematopoiesis: concordant findings from multiple studies

Genovese et al., NEJM 2014
Xie et al., Nat Med, 2014
McKerrell et al., Cell Rep 2015
Clonal Hematopoiesis of Indeterminate Potential (CHIP)

- Features:
  - Absence of definitive morphological evidence of a hematological neoplasm
  - Does not meet diagnostic criteria for PNH, MGUS or MBL
  - Presence of a somatic mutation associated with hematological neoplasia at a variant allele fraction of at least 2%
  - Odds of progression to overt neoplasia are approximately 0.5-1% per year, similar to MGUS

Steensma et al., Blood 2015
Clonal hematopoiesis is associated with reduced overall survival.

Cox proportional hazards models which included age, gender, and diabetes status as covariates, with results for cohorts analyzed as a fixed-effects meta-analysis.
Clonal hematopoiesis is associated with higher risk of heart attack and stroke.

Coronary heart disease

- No mutation, n=2,912
- Mutation, n=118

HR 2.0, 95% CI 1.2-3.4, p=0.018

Stroke

- No mutation, n=3,094
- Mutation, n=123

HR 2.6, 95% CI 1.4 to 4.8, p=0.003

Regression models were adjusted for age, sex, BMI, lipids, blood pressure, and smoking.
Replication in additional cohorts

Jaiswal et al., NEJM 2017
CHIP and early-onset MI

<table>
<thead>
<tr>
<th>Clonal hematopoiesis and early onset MI</th>
<th>OR (CI 95%)</th>
<th>No. with MI/ No. at risk</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATVB, no mutation (referent)</td>
<td></td>
<td>1729/3308</td>
<td></td>
</tr>
<tr>
<td>ATVB, mutation</td>
<td>5.4 (2.3-13)</td>
<td>37/43</td>
<td>0.0002</td>
</tr>
<tr>
<td>PROMIS, no mutation (referent)</td>
<td></td>
<td>2543/3905</td>
<td></td>
</tr>
<tr>
<td>PROMIS, mutation</td>
<td>3.4 (1.8-6.5)</td>
<td>52/65</td>
<td>0.0002</td>
</tr>
<tr>
<td>Fixed-effects meta-analysis</td>
<td>4.0 (2.4-6.7)</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Jaiswal et al., NEJM 2017
Experimental examination of CHIP and cardiovascular disease

8-12 week old
Vav1-Cre, TET2 fl/fl
Vav1-Cre (control)

8 week old
WT ldlr-/-
female

BMT

Diet:
1.25% cholesterol

harvest
Descending aorta lesion area is larger in Tet2−/− recipients

- Tet2 fl/fl, Vav1-Cre
- Tet2 +/-fl, Vav1-Cre
- Vav1-Cre
CHIP and therapy-related malignancies

401 samples from non-Hodgkin’s lymphoma patients undergoing autologous stem cell transplantation

Number affected  Number at risk
0               10
3               28
12              50
35              143
61              148
9               22

Gibson et al., JCO 2017
CHIP and therapy-related malignancies

A

Cumulative Incidence of TMN

Probability of TMN

CHP

No CHIP

P=0.002

Years

B

Overall Survival

Percent survival

P<0.001

Years

Gibson et al., JCO 2017
Clonal Hematopoiesis of Indeterminate Potential (CHIP) summary

- Common, age-associated, pre-malignant condition
- Most commonly mutated genes include *DNMT3A, TET2, ASXL1, TP53*
- Associated with increased overall mortality
  - Increased risk of hematologic malignancy
  - Increased risk of therapy-related malignancy
  - Increased risk of cardiovascular disease
Prognosis

Prediction of therapeutic response
Distribution of Mutations in MDS

Bejar et al., *NEJM* 2011
Bejar et al., *JCO* 2012
137/439 (31.2%) Samples carry a mutation in one or more of these genes

<table>
<thead>
<tr>
<th>Mutational Status - Present vs. Absent</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>TP53</em> Mutation</td>
<td>2.48 (1.60-3.84)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><em>EZH2</em> Mutation</td>
<td>2.13 (1.36-3.33)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><em>ETV6</em> Mutation</td>
<td>2.04 (1.08-3.86)</td>
<td>0.029</td>
</tr>
<tr>
<td><em>RUNX1</em> Mutation</td>
<td>1.47 (1.01-2.15)</td>
<td>0.047</td>
</tr>
<tr>
<td><em>ASXL1</em> Mutation</td>
<td>1.38 (1.00-1.89)</td>
<td>0.049</td>
</tr>
</tbody>
</table>

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<tr>
<th>Mutational Status - Present vs. Absent</th>
<th>Age</th>
<th>IPSS Risk Group</th>
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</tr>
</thead>
<tbody>
<tr>
<td>≥55 yrs vs. &lt;55 yrs</td>
<td>1.81 (1.20-2.73)</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>Int1 vs. Low</td>
<td>2.29 (1.69-3.11)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Int2 vs. Low</td>
<td>3.45 (2.42-4.91)</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>High vs. Low</td>
<td>5.85 (3.63-9.40)</td>
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Clinical genetics for myeloid neoplasms

Prognosis

Prediction of therapeutic response
Cohort: 1514 MDS patients

- Broadly representative: 130 transplant centers
- Uniform diagnosis: MDS (<20% blasts)
- No exclusions based on patient or transplant variables

<table>
<thead>
<tr>
<th>Age</th>
<th>Conditioning intensity</th>
<th>Graft type</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RIC (38%)</td>
<td>UCB (11%)</td>
</tr>
<tr>
<td></td>
<td>MAC (52%)</td>
<td>BM (15%)</td>
</tr>
<tr>
<td></td>
<td>NST (9%)</td>
<td>PBSC (74%)</td>
</tr>
</tbody>
</table>

Lindsley et al., *NEJM* 2017
Multivariable Model for Overall Survival

MDS

TP53 mutation

Age ≥ 40

RAS pathway mutation

JAK2V617F

No RAS pathway mutation

No JAK2 or RAS pathway mutation

≥ 1 High-risk feature

No high-risk features

No TP53 mutation

Age < 40

High risk features
1. Therapy-related MDS
2. Platelets < 30 x 10^9/L at HCT
3. Blasts ≥ 15% at diagnosis
TP53 mutations lead to relapse and poor survival

MDS

TP53 mutation
Median OS = 8 months

No TP53 mutation

Survival

No TP53 mutation
p < 0.0001

TP53 mutation

Relapse

TP53 mutation
p < 0.0001

No TP53 mutation
Survival

All patients < 40 years old

Somatic TP53 mutations

\[
p < 0.001 \\
p = 0.01
\]

Lindsley et al., NEJM 2017
Summary

**TP53 mutations**
- Poor prognosis
- No benefit to myeloablative conditioning

**RAS pathway and JAK2 mutations**
- Poor prognosis in patients ≥ 40 without TP53 mutations
- RAS: high early relapse, improved OS and relapse with MAC
- JAK2: high NRM, no decrease in NRM with RIC

**SBDS mutations: unrecognized Shwachman-Diamond Syndrome**
- Common in young adults (4%)
- Poor prognosis, somatic TP53 mutations
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