Age-related changes in hematopoiesis

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Clonal hematopoiesis

HSCs acquire 1 protein-coding mutation per decade (Welch et al. Cell 2012)

By age 70, 1.4 million coding mutations in HSCs

Presaged by work in skewed XCI (Busque, Gilliland, Levine, et al.) and pre-leukemic HSCs in AML (Majeti, Slush et al.)
A new clinical entity: Clonal Hematopoiesis of Indeterminate Potential (CHIP)

- Defined as a cancer-associated, clonal mutation with VAF>2% in the blood of healthy persons without a known hematologic disorder

- Is common with aging (present in at least 10% of all persons age>70)

- Associated with increased relative risk of malignancy, risk of progression is 1% per year

Jaiswal et al., *NEJM* 2014  
Genovese et al., *NEJM* 2014  
Xie et al., *Nat Med* 2014  
Bick et al., *Biorxiv* 2019  
McKerrell et al., *Cell Reports* 2015  
Coombs et al., *Cell Stem Cell* 2017
A new clinical entity: Clonal Hematopoiesis of Indeterminate Potential (CHIP)

- Defined as a cancer-associated, clonal mutation with VAF>2% in the blood of healthy persons without a known hematologic disorder

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Mutations persist in mature blood lineages

Hematopoietic stem cell

Lymphoid progenitors

T-Cell

B-Cell

Monocyte

Neutrophil

Megakaryocyte

Erythrocyte

Acute myeloid leukemia
Myelodysplastic syndrome
Lymphoma

Alteration of effector immune function?

Chronic diseases of aging?
CHIP is associated with higher risk of incident coronary heart disease

Jaiswal et al., *NEJM* 2014

From Jaiswal and Libby, *Nat Rev Card* 2019

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 50–59 years</td>
<td>2.20 (1.32–3.69)</td>
</tr>
<tr>
<td>Age 60–69 years</td>
<td>2.41 (1.44–4.02)</td>
</tr>
<tr>
<td>Age ≥70 years</td>
<td>6.27 (3.77–10.42)</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.68 (0.50–0.93)</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td>2.18 (1.62–2.94)</td>
</tr>
<tr>
<td>Former or current smoker</td>
<td>1.40 (1.04–1.90)</td>
</tr>
<tr>
<td>Hypertension stage II–IV</td>
<td>1.20 (0.89–1.62)</td>
</tr>
<tr>
<td>Total cholesterol level &gt;200 mg/dl</td>
<td>1.40 (1.04–1.88)</td>
</tr>
<tr>
<td>HDL-cholesterol level &lt;35 mg/dl</td>
<td>1.46 (0.98–2.18)</td>
</tr>
<tr>
<td>HDL-cholesterol level &gt;60 mg/dl</td>
<td>0.77 (0.52–1.13)</td>
</tr>
<tr>
<td>Presence of CHIP</td>
<td>1.82 (1.15–2.89)</td>
</tr>
</tbody>
</table>
DNA methylation clocks

Field et al., Mol Cell 2018

Horvath/IEAA
353 CpGs
Works in most tissues

Hannum/EEAA
71 CpGs
Influenced by
blood cell composition

GrimAge
1030 CpGs
Smoking
Blood biomarkers

Skin and Blood
391 CpGs
Works in most tissues

PhenoAge
513 CpGs
Mortality/disease

"Age acceleration"

Older epigenome
Younger epigenome

Cell intrinsic (proliferation)  Cell extrinsic (biomarkers)
Could CHIP be a modifying factor in many non-neoplastic age-related diseases?
Does CHIP have any association with biological aging?
TOPMed CHIP-Methylation Project

Trans-Omics for Precision Medicine
(>100K participants)

Whole genome sequencing

CHIP and methylation age acceleration
~5000 people

Blood DNA methylation arrays
CHIP is strongly associated with epigenetic age acceleration

Mendelian randomization supports a causal role for CHIP in epigenetic aging

Results similar to Robertson et al., Current Biology 2019

Nachun et al., Aging Cell 2021
Does the combination of CHIP plus epigenetic age predict outcomes?

**Cohorts:**
- FHS (1374)
- JHS (1725)
- WHI (1235)

**Defined ‘AgeAccel’:**
>0 age acceleration in a clock

- Horvath
- IEAA
- Skin and Blood
- Hannum
- EEAA
- PhenoAge
- GrimAge

**Analysis:**
- All-cause mortality
- Cox proportional hazards

Looking for interaction effects in regression model (CHIP*AgeAccel) to identify the most predictive clocks.
Does the combination of CHIP plus epigenetic age predict outcomes?

<table>
<thead>
<tr>
<th>Clock</th>
<th>Interaction Coefficient</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horvath</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>IEAA</td>
<td>-0.26</td>
<td>0.31</td>
</tr>
<tr>
<td>Skin/Blood</td>
<td>-0.07</td>
<td>0.81</td>
</tr>
<tr>
<td>Hannum</td>
<td>0.56</td>
<td>0.050</td>
</tr>
<tr>
<td>EEAA</td>
<td>0.15</td>
<td>0.58</td>
</tr>
<tr>
<td>Pheno</td>
<td>-0.14</td>
<td>0.59</td>
</tr>
<tr>
<td>Grim</td>
<td>0.48</td>
<td>0.097</td>
</tr>
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Defined ‘AgeAccelComb’:

- AgeAccelHannum > 0
- AND
- AgeAccelGrim > 0

24.3% of CHIP- (989/4065)
39.4% of CHIP+ (106/269)

Does being AgeAccelComb+ affect outcomes differently depending on CHIP status?

Time to death ~ Age + Sex + Race + T2D + LDL + HDL + TG + SBP + smoking + CHIP * AgeAccel

bicor = 0.235
R² = 0.056
Nearly all risk for adverse events resides in ~40% of CHIP carriers

<table>
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<th>Without methylation data</th>
<th>Time to Death</th>
<th>HR (CI95)</th>
<th>p-value</th>
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<tr>
<td>CHIP- (referent)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHIP+</td>
<td>1.27 (0.97-1.65)</td>
<td>0.077</td>
<td></td>
</tr>
<tr>
<td>AgeAccelComb- (referent)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHIP-</td>
<td>1.66 (1.40-1.97)</td>
<td>3.2 x 10^-6</td>
<td></td>
</tr>
<tr>
<td>CHIP+ AgeAccelComb+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHIP-</td>
<td>0.78 (0.53-1.13)</td>
<td>0.20</td>
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</tr>
<tr>
<td>CHIP+ AgeAccelComb+</td>
<td>2.90 (1.98-4.24)</td>
<td>4.1 x 10^-8</td>
<td></td>
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P for interaction = 0.004

10 year risk
- CHIP-/AgeAccelComb+ 24.5%
- CHIP-/AgeAccelComb- 19.2%
- CHIP+/AgeAccelComb+ 47.9%
- CHIP+/AgeAccelComb- 15.9%

Age >65 and no CHD at baseline

Time to death ~ Age + Sex + Race + T2D + LDL + HDL + TG + SBP + smoking + CHIP*AgeAccelComb
Summary

- Mutations accumulate steadily over time in stem cell compartments, creating diversity and material for natural selection.
- CHIP is common in aging.
- CHIP is associated with increased risk of cancer and CVD.
- CVD appears to be due to enhanced inflammation.
- The combination of CHIP and epigenetic aging identifies a high-risk population.
- CHIP carriers may preferentially respond to drugs targeting inflammatory pathways.

Adapted from Jaiswal and Libby, Nat Rev Card 2019.
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