The Clonal Degeneration of Hematopoetic Aging

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Clonal Hematopoiesis and Blood-Cancer Risk Inferred from Blood DNA Sequence

Age-Related Clonal Hematopoiesis Associated with Adverse Outcomes

Genovese et al. NEJM 2014 371(26) 2477-87. PMID 25426838

Jaiswal et al. NEJM 2014 371(26) 2488-98. PMID 25426837
Hypothesis
Deeply sequence leukocyte exomes from previously collected cohorts to assess for the presence of subclonal mutations and their association with subsequent neoplasia, age and other clinical characteristics.
**Approach:** look for subclonal mutations

- 100%
- 92%
- 8%
- 50%
- 50%
- 50%
- 46%
- 4%
Approach

Depth: 84x (13-144x)
Allele ratio sensitivity 3.5%
Subclone sensitivity 7%

Genovese

(Jaiswal)
Sample selection

Total leukocyte compartment DNA

**Genovese**
- Swedish schizophrenia, bipolar and control cohort
- 12,380 patients (11,164 w/FU)
- Screened for all subclonal mutations then stratified by candidates

**Jaiswal**
- 22 cohort studies: longevity, type II diabetes and Jackson Heart Study
- 17,182 patients (3,342 w/FU)
- Focused on 160 candidate heme malignancy candidates genes
Findings

**Genovese**
- 3111 mutations across the exome
- About 25% of individuals
- Mutations per subclone ~1

**Jaiswal**
- 805 mutations in 73 genes
- 746 (4.3%) individuals
- Mutations per subclone ~1
Somatically-derived clones increase with age

18.4% of 90-108 y/o
Specific genes more commonly bear mutations

- **DNMT3A**: DNA methyltransferase, increased pluripotency, growth advantage
- **ASXL1**: Chromatin remodeling, development
- **TET2**: Methylcytosine deoxygenase, increased self renewal, growth advantage
- **PPMD1**: Regulator of p53, LOF disrupts normal checkpoint inhibition
Clones associate with higher risk of malignancy

RR: 11x

RR: 12.9x

Genovese

Jaiswal

<table>
<thead>
<tr>
<th>Category</th>
<th>No. of Patients</th>
<th>Hazard Ratio for Hematologic Cancer (95% CI)</th>
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<tbody>
<tr>
<td>No mutations</td>
<td>8783</td>
<td>1.00 (1.00–1.00)</td>
</tr>
<tr>
<td>CH-UD</td>
<td>170</td>
<td>11.34 (3.44–37.41)</td>
</tr>
<tr>
<td>CH-CD</td>
<td>269</td>
<td>13.73 (5.74–32.83)</td>
</tr>
<tr>
<td>CH</td>
<td>439</td>
<td>12.89 (5.78–28.72)</td>
</tr>
</tbody>
</table>
Etiologic relationship neoplasia

- Recurrently seen in human hematologic malignancy (COSMIC)
- Recurrent, independent mutations in multiple cohorts
- Plausible mechanism, xenograft and knockout/in mouse studies
- Enrichment for nonsynonomous mutations
- Larger clones associated with greater risk of neoplasia
- Median number of mutations per clone (~1) vs that with AML/MDS (~5)
- Distinct absence of major leukemia-associated genes (FLT3, NPM1 etc)
Selected example of temporal clonal evolution

Genovese
Majority of clones do not lead to leukemia

- Genovese: 12.9-fold relative risk of leukemia but absolute risk only ~1% per year.

- Jaiswal:
  - 13 subjects with clonal mutations (17) at baseline had available sample 4-8 yr later
  - 10 mutations with same clone size at follow-up
  - 7 mutations with increased clone size
  - 2 subjects with new mutations
  - Zero leukemias

- Other examples of clonal field defects:
  - Liquids: MGUS, B cell lymphocytosis, CLL, MDS
  - Solids: Barretts Esophagus, ulcerative colitis, certain lung, bladder, oropharynx
Clones portend higher risk of all-cause mortality

Attributed to leukemia and smoking

Not explained by leukemia
2x RR coronary artery disease
2.6X RR ischemic stroke
Clinically unhelpful metric (at present)

• Strongest association is with age, not disease

• Poor sensitivity: 48%, 59% of those who developed leukemia w/o prior clones

• Poor specificity: of 3342 patients, 134 (4%) had clonal mutations yet only 16 (11.9%) developed cancers during course of Jaiswal study

• Cost, number needed to screen, age w/most potential benefit least likely affected

• Absence of clinical actionability:
  • No proven risk-reduction strategies, potential harms abound
  • Unknown benefits of early detection of leukemia itself
  • Patient age: all organisms are mortal

• Incidentaloma that is hard to ignore
Many open biologic and clinical questions

- Mechanistic basis of clonal expansions: drivers of neoplasia or unmasked symptom of unhealthy stem cell compartment? Benign boosters?
- Clonal definition by passengers: identify drivers outside of the exome
- Prognostic difference of malignancies arising from preneoplastic fields
- Longer follow-up of outcomes, dedicated longitudinal collection
- Prevention strategies. Surrogate metric for clinical trials?
- Basis of increase in all cause mortality not explained by leukemia. Cardiovascular disease: pathogenic atherosclerosis vs. chronic inflammation?
- Substratification of risk by specific drivers, leukocyte subsets, coincidence of mutations (digital single cell assays), temporal dynamics.
- Greater depth, greater accuracy
- Psychological, sociological, financial implications
- Fundamental relationship with aging