CLONAL HEMATOPOIESIS: A PATHWAY TO CANCER, A PATHWAY TO HEART DISEASE

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Clonal Hematopoiesis:  
A pathway to cancer,  
A pathway to heart disease

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Question

Which of the following statements about clonal hematopoiesis are true?

A) Clonal hematopoiesis results from **acquired** genetic mutations in the blood of normal individuals

B) Clonal Hematopoiesis increases the risk of hematologic malignancy, but the **absolute risk** is low

C) Clonal Hematopoiesis increases risk of atherosclerotic cardiovascular disease **2-4 fold**

D) Clonal Hematopoiesis increases risk of CHF in **mouse models**

E) All of the above
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Clonal Hematopoiesis:  
A pathway to cancer,  
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Acquired genetic mutations associated with acute myeloid leukemia (AML) are found in the blood cells of normal individuals:

- Increase the risk of developing
  - Hematologic malignancies
  - Atherosclerotic cardiovascular disease
  - Heart failure
Acute myeloid leukemia (AML) – an aggressive malignancy

AML

Normal Adult bone marrow

Cytogenetics are prognostic in AML

Survival

Cumulative relative survival

0.0000
0.0010
0.0020
0.0030
0.0040
0.0050
0.0060
0.0070
0.0080
0.0090
0.0100

Years since diagnosis

1973-1980
1981-1988
1989-1996
1997-2005
Molecular Mutations in Cytogenetically Normal AML

- Prognostic markers
- Therapeutic targets
- Minimal residual disease markers
Mutations associated with AML found in normal hematopoietic cells

AML cells

Normal T cells

HSC niche

Differentiated Lineages

AML Diagnosis


Cell Stem Cell 2014 14, 421-422DOI: (10.1016/j.stem.2014.03.008)
Clonal Hematopoiesis – increases with age

- Clonal hematopoiesis increases with age
- >10% incidence in age >70 in normal population
- More frequent if look deeper
- Most frequent mutations: DNMT3A, TET2, ASXL1, JAK2 ATM, PPM1D, TP53, SRSF2

Variant allele frequency (VAF)
- Proportion of alleles with mutation
- VAF = 3.5% in this study
- Heterozygote mutations = 7% of cells

Clonal hematopoiesis is more common after chemotherapy

Swisher et al, JAMA Oncol 2016
Clonal Hematopoiesis – a pathway to cancer


VAF - 3.5%
Clonal hematopoiesis increases risk for cardiac disease/myocardial infarction

Prospective cohorts, median age 60-70y

- **MDC study** – median age 60
  - Follow-up 18 years
  - Case control studies with patients in the prospective Malmo Diet and Cancer (MDC) study
  - 2.0 x increased risk of CVD

Retrospective case-control cohorts, <50y

- **PROMIS study** – ages 40-50
  - Exome sequencing from retrospective case control
  - PROMIS (Pakistan Risk of MI study) study to evaluate early MI (age 40-50) clonal hematopoiesis
  - 3.4 x increased risk of CVD

VAF >10%

JAK2V617F 12.1 x risk

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Clonal hematopoiesis increases atherosclerosis in a mouse model.

Atherosclerosis prone
Ldlr (LDL receptor)
-/- mice

17 weeks

C Aortic Atherosclerosis, According to Tet2 Status

D Involvement of Aorta, According to Tet2 Status

How to does TET2 deficiency/mutation lead to atherosclerosis

- TET2
- NLRP3: Inflammasome complex
- IL-1β: Transcription, processing, secretion

- Endothelial activation
- Endothelial adhesion markers
- Monocyte recruitment to endothelium

Science 2017;355:842-847
Clonal hematopoiesis and heart failure

10% TET2 -/- cells

10% TET2 wt cells

LAD ligation
Or
Transverse aortic constriction

10% TET2 KO
• Decreased LV volume
• Decreased EF
• Increased fibrosis
• Increased IL1B

Prevented with the inflammasome inhibitor MCC950
Questions:

A) Is there a role for inflammasome inhibitors or other anti-inflammatory strategies for atherosclerosis secondary to clonal hematopoiesis?

B) Is there a role for the anti-IL1β antibody canakinumab in atherosclerosis secondary to clonal hematopoiesis?
Treating clonal hematopoiesis with organges

In mice:
- Alters DNA methylation
- Decreases leukemic growth

Dose of vitamin C = 5.6g i.v daily x 10d

?? Effects on clonal hematopoiesis
Conclusions/ Key learnings

• Acquired genetic mutations associated with AML are found in the blood of normal individuals – Clonal Hematopoiesis

• Clonal Hematopoiesis increases the risk of hematologic malignancy, but absolute risk is low

• Clonal Hematopoiesis increases risk of atherosclerotic cardiovascular disease and perhaps congestive heart failure
Important questions in the field

• Which ARCH mutations are most predictive of cardiovascular disease risk

• What amount of clonal hematopoiesis (VAF %) is required to increase the risk of cardiovascular disease

• How does clonal hematopoiesis evolve over time and who is at increased risk?

• How should we treat patients with ARCH and increased risk of cardiovascular disease
  – Cardiovascular treatment
  – Hematologic treatment to reduce ARCH clones
Trends in the next 3 years

- Cheaper and tailored genetic profiling assays for detection of clonal hematopoiesis
- Screening of high populations (e.g.: cancer survivors)
- Relationships to diseases beyond atherosclerotic cardiovascular disease
- Treatment of high risk patients
Cardiology-Hematology Collaboration

- Dedicated Clonal Hematopoiesis clinic

- Trials evaluating effects of clonal hematopoiesis on cardiovascular biology/pathology

- Trials evaluating therapy to prevent cardiac disease, decrease inflammation, and target the genetic subclones.