Transforming Mutations in Myeloid Leukaemia of Down Syndrome

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Multistep Leukaemogenesis: Co-operating mutations in cancer

- Cancer is a genetically complex disease. Often caused by step-wise acquisition of somatic mutations.

- Understanding the function and co-operativity of these mutations is key to cancer biology and therapeutics.

- Blood cancers, such as Acute Myeloid Leukaemia, often simpler than solid tumours.

- **Myeloid Leukaemia of Down Syndrome (ML-DS):** a model for multistep leukaemogenesis.
Myeloid Leukaemia of Down Syndrome (ML-DS): a model for multistep leukaemogenesis

1. Abnormal Fetal Haemopoiesis in T21

Fetal cell

+21

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Roy et al., 2012 PNAS
Myeloid Leukaemia of Down Syndrome (ML-DS): a model for multistep leukaemogenesis

1. Abnormal Fetal Haemopoiesis in T21

2. Acquired GATA1s Mutation

Alford et al., 2011 Blood
Roberts et al., 2013 Blood
Myeloid Leukaemia of Down Syndrome (ML-DS): a model for multistep leukaemogenesis

1. Abnormal Fetal Haemopoiesis in T21
2. Acquired GATA1s Mutation
3. Additional mutation(s)

Yoshida et al., 2013 Nature Genetics
Nikolaev et al., 2013 Blood
Labuhn, Perkins et al., Cancer Cell 11-07-2019
Transforming mutations in Myeloid Leukaemia of Down Syndrome

1. Abnormal Fetal Haemopoiesis in T21

2. Acquired GATA1s Mutation

3. Additional mutation(s)

- Mutational Landscape
- Functional Characterisation
- Mechanism of cooperation

Labuhn, Perkins et al., Cancer Cell 11-07-2019
Transforming Mutations in ML-DS:

- Blood and BM samples
  - 111 TAM
  - 141 ML-DS samples
- 12 matched TAM and ML-DS pairs
- 20 samples exome sequenced
- Targeted resequencing (baits at Sanger Centre and access array Vyas lab)

Labuhn, Perkins et al., Cancer Cell 11-07-2019
Transforming mutations in ML-DS

Labuhn, Perkins et al., Cancer Cell 11-07-2019
Transforming mutations in ML-DS

ML-DS enriched for additional somatic variants

Labuhn, Perkins et al., Cancer Cell 11-07-2019
What is the functional significance of these variants?

JAK/MPL variants reported in TAM samples shown to be non functional. Those present in ML-DS resulted in gain of function.
What is the functional significance of these variants?

Identified novel hotspot in **CSF2RB**. Functionally oncogenic.

**CSF2RB**
Transforming mutations in ML-DS

Multiplex in vivo loss of function screen

Cas9-knock-in fetal Liver

Fetal liver cells

Gata1s mutant cells

ML-DS?

Total = 232 mutations in 141 ML-DS patients

Total = 104 mutations in 38 leukemic mice

- cohesin complex
- epigenetic regulators
- signaling pathways
- transcription factors
- others

Labuhn, Perkins et al., Cancer Cell 11-07-2019
Co-operating mutations in ML-DS

1. Trisomy 21

Fetal Liver → TAM

2. Gata1s

1. Trisomy 21

TAM → ML-DS

2. Gata1s

3. Cooperating mutation(s)
   - Cohesin
   - Epigenetic regulators
   - Signalling molecules
GATA1s mutations in TAM and ML-DS

- Fetally acquired
- Exclusive production of GATA1s
- Uniform (exon 2/3)
- Necessary for development of TAM
- Not leukaemogenic in the absence of trisomy 21
- Disappear with resolution of TAM/ML-DS clone

Alford et al. 2011 Blood
Roberts et al. 2013 Blood
Ahmed et al. 2004 Blood
Hollanda et al. 2005 Nature Genetics
Conclusions

• Understanding mutational cooperativity is complex

• Cancer may result from multiple subtle effects coming together in a cell or population of cells to together cause proliferation and differentiation block

• Ongoing questions
  • Why are Gata1s mutations so common in DS?
  
  • Why is ML-DS enriched for cohesin gene mutations?
  
  • What is the role of T21?
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