INFECTION, IMMUNE RESPONSES AND THE AETIOLOGY OF CHILDHOOD LEUKAEMIA

Mel Greaves
A MINIMAL 2 STEP MODEL FOR ACUTE LYMPHOBLASTIC LEUKAEMIA

1

Chr. translocations
hyperdiploidy
B lymphoid stem cell

birth

2

COVERT
PRE-LEUKAEMIA

other mutations

L

3-5 yrs
PRE-NATAL ORIGINS OF PAEDIATRIC LEUKAEMIA

- Clonal relationships of concordant leukaemia in monozygotic twins
- Retrospective molecular scrutiny of archived neonatal blood spots of children with leukaemia
- Molecular screening of cord blood of new borns
EARLY OR INITIATING EVENTS IN LEUKAEMOGENESIS

- Foetal haemopoiesis (liver / bone marrow?)
- Chromosome translocation / gene fusions
  - MLL-AF4
  - TEL-AML1
  - AML1-ETO
- Chromosomal hyperdiploidy
- Chromosomal instability
- Mutations - GATA1 in TMD / AML in Down’s
**TEL-AML1 FUSION IS AN INITIATING EVENT BUT IS INSUFFICIENT FOR LEUKAEMOGENESIS**

- Concordance rate in monozygotic twins is \(~10\%\)
  (Greaves et al, 2003, Blood, 102: 2321-2333)

- Mice transgenic for *TEL-AML1* are *pre-leukaemic*
  (Tsuzuki et al, 2004, PNAS, 101: 8443-8448)

∴ secondary, post-natal events are critical
FREQUENCY AND RISK OF ACUTE LYMPHOBLASTIC LEUKAEMIA?

Risk of ALL ~ 1 in 2,000
Risk of ALL with TEL-AML1 ~ 1 in 10,000
Risk of TEL-AML1+ cord blood ~ 1 in 100

LEUKAEMIA IS INITIATED, PRE-NATALLY AT ~100 x THE DISEASE RATE

POST-NATAL SECONDARY EVENTS ARE THE BOTTLENECK FOR LEUKAEMIA AETIOLOGY
NATURAL HISTORY OF PAEDIATRIC ACUTE LEUKAEMIAS

1°
INITIATION
(common)

Chr. translocation
hyperdiploidy

birth

2°
Rare TRANSITION to
ALL / AML

1%

Gene deletion/
mutation

2-15 yrs
## MOLECULAR SCREENING FOR VIRAL SEQUENCES IN CHILDHOOD ALL

### Virus Screened For

- Polyomaviruses JC and BK
- Parvovirus B19
- Human herpesvirus family (HHV4, 5, 6, 7 and 8)
- Bovine leukaemia virus
- TT virus
- Exogenous microbial sequences

### Screening Method

- Specific PCR*
- Specific PCR
- PCR using degenerate primers*
- Southern blotting
- Specific PCR
- Representative difference analysis*

*MacKenzie J, Jarrett RF et al
INFECTION-BASED HYPOTHESES FOR THE AETIOLOGY OF CHILDHOOD LEUKAEMIA

Greaves M (1988) *Leukemia*

The ‘delayed infection’ hypothesis

**Model**:

- Timing of common infections critical (- delay?)
  cf. hygiene hypothesis for allergies and type 1 diabetes

- Abnormal immune response facilitates expansion of pre-leukaemic clone

- Genetic susceptibility impacts on risk
A CAUSAL MECHANISM FOR CHILDHOOD LEUKAEMIA

CANDIDATE EXPOSURES?

1

TEL-AML1
Hyperdiploidy

ABNORMAL IMMUNE RESPONSE TO COMMON INFECTIONS?

2

TEL\text{del}
FLT-3\text{mut}

IMMUNE RESPONSE GENES?

INHERITED SUSCEPTIBILITY?

ALL
EPIDEMIOLOGICAL EVIDENCE SUPPORTING THE ‘DELAYED INFECTION’ HYPOTHESIS

- Increased common infections in *infancy* are **protective**

- Increased social contacts in *infancy* are **protective**
  - parity
  - attendance at playgroups

(- proxies for infection)
MODEL 2006

Timing

aberrant IR to infection

cytokine ‘selection’

Genetics

covert pre-leukaemia

1%

TEL-AML1

TEL^{del} etc

ALL