The pre-clinical evolution of haematological malignancies

Grace Collord

King's College

University of Cambridge

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Declaration

I hereby declare that this dissertation is my own work and that any work done in collaboration with others is explicitly indicated in the text. This work does not contain any material substantially similar to work I have previously submitted, or am in the process of preparing, for any qualification at any institution. This dissertation does not exceed 60,000 words in length.

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Summary

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Cancer-associated somatic mutations frequently drive clonal expansions in normal ageing tissues. However, the factors governing whether pre-cancerous cells transform into cancer are poorly understood, hindering identification of clones that are clinically significant rather than benign sequelae of ageing. The main aim of this dissertation has been to explore this process in the haematopoietic system, where leukaemia-associated mutations are detectable in >10% of individuals over the age of 50. This phenomenon, termed clonal haematopoiesis (CH), is associated with an increased risk of blood cancers, though only a small minority of individuals progress.

Acute myeloid leukaemia (AML) is the commonest acute leukaemia in adults, and usually presents abruptly with complications of bone marrow failure. Using deep targeted sequencing of stored blood DNA samples from individuals who went on to develop AML and controls, we identified features of CH that predict leukaemic progression. The number, type and burden of genetic changes, as well as certain clinical variables, were predictive of AML-free survival. Examining the pre-clinical evolution of lymphoid malignancies using a similar study design and broader sequencing approach also revealed genetic and clinical features predictive of malignant transformation.

The final part of this study investigates the prevalence of clonal haematopoiesis in childhood cancer survivors treated with intensive chemo- or radiotherapy. In contrast to adult cancer patients, the prevalence of CH in children is not dramatically increased by cytotoxic treatment.

Collectively, these findings provide proof of principle that benign and pre-malignant clonal expansions in normal blood (and perhaps other tissues) may be distinguishable years prior to overt malignant transformation. This could in future enable earlier detection of those at high risk of blood cancers, and stimulate research into possible interventions to reduce the risk of progression.

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Abbreviations

ALL	Acute lymphoblastic leukaemia
AML	Acute myeloid leukaemia
AUC	Area under the curve
bp	Base pair
BMI	Body mass index
C	Concordance
CCA	Choriocarcinoma
cDNA	Complementary deoxyribonucleic acid
CH	Clonal haematopoiesis
CH-PD	Clonal haematopoiesis with putative driver mutations
CHIP	Clonal haematopoiesis of indeterminate significance
CLL	Chronic lymphocytic leukaemia
CML	Chronic myeloid leukaemia
CNA	Copy number aberration
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DC	Discovery cohort
DNA	Deoxyribonucleic acid
ES	Ewing sarcoma
FBC	Full blood count
FFPE	Formalin-fixed paraffin-embedded
HSC	Haematopoietic stem cell
HSCT	Haematopoietic stem cell transplant
HSPC	Haematopoietic stem and progenitor cell
KM	Kaplan-Meier
GCT	Germ cell tumour
HDL	High-density lipoprotein
HL	Hodgkin lymphoma
HSC	Haematopoietic stem cell
HSCT	Haematopoietic stem cell transplant
LCH	Langerhans cell histiocytosis
LDL	Low-density lipoprotein
LL	Lymphoblastic lymphoma
LOH	Loss of heterozygosity
Mb	Megabase
MBL	Monoclonal B-cell lymphocytosis
MDS	Myelodysplastic syndrome
MGUS	Monoclonal gammopathy of undetermined significance

MM	Multiple myeloma
MPN	Myeloproliferative neoplasm
NGS	Next-generation sequencing
NHL	Non-Hodgkin lymphoma
NB	Neuroblastoma
NPC	Nasopharyngeal carcinoma
NRSTS	Non-rhabdomyosarcoma soft tissue sarcoma
PCR	Polymerase chain reaction
RBC	Red blood cell
RDW	Red cell distribution width
RNA	Ribonucleic acid
sAML	Secondary AML
SBP	Systolic blood pressure
SNP	Single nucleotide polymorphism
SNV	Single nucleotide variant
RMS	Rhabdomyosarcoma
TC	Total cholesterol
T-ALL	T-cell acute lymphoblastic leukaemia
t-AML	Therapy-related AML
t-MN	Therapy-related myeloid neoplasm
VAF	Variant allele fraction
VC	Validation cohort
WBC	White blood cell
WT	Wilms tumour