ICR The Institute of Cancer Research

PhD Project Proposal

Funder details

Studentship funded by:	ICR

Project details

Project title:	Investigating the functions of histone acetylation in genome organization and leukemogenesis

Supervisory team

Primary Supervisor:	Alex Radzisheuskaya
Associate Supervisor(s):	TBC
Secondary Supervisor:	Jessica Downs

Divisional affiliation

Primary Division:	Cancer Biology
Primary Team:	Chromatin Biology
Site:	Chelsea

Project background

In eukaryotic cells, the DNA inside the nucleus is hierarchically packaged as chromatin. The nucleosome represents the first level in this hierarchy and consists of a DNA segment wrapped around an octamer of four histone proteins with side chains subject to extensive post-translational modifications. At higher organizational levels, nucleosomes are assembled into fibers, loops, domains, and compartments, which together form a dynamic structure regulating all the DNA-dependent processes and safeguarding genome integrity1. The importance of chromatin regulation in controlling cell phenotype is highlighted by altered epigenomes and frequent mutations in genes encoding chromatin-modifying enzymes in cancer cells2. Despite excellent recent progress in chromatin biology, a detailed mechanistic understanding of how chromatin organization contributes to genome stability, gene expression and cancer is still lacking.

Acetylation of histone tails is generally assumed to decompact chromatin and thus provide local DNA access for genomic processes. The importance of histone acetylation can be demonstrated by the fact that 12 out of 16 histone acetyltransferases (or HATs) have embryonic-lethal KO phenotypes. Moreover, misregulation of HAT function is known to cause developmental disorders and drive cancer development3. Despite these strong phenotypes, the data on the functions of HATs in mammalian cells remain largely correlative, and the consequences of site-specific histone acetylation are not known. Thus, it would be important to gain a detailed mechanistic understanding of the function of histone acetyltransferases and their histone products.

This project is focused on investigating the molecular functions of histone acetylation in the context of acute myeloid leukaemia.

Project aims

- Generate and characterize novel mouse leukaemia models driven by the oncogenic histone acetyltransferases
- Investigate the molecular mechanisms underlying the development of leukaemia in the established models
- Explore specific vulnerabilities of the established leukemic cell lines in vitro and in vivo

Research proposal

Acute myeloid leukaemia (AML) is a malignant blood disorder characterized by the uncontrolled proliferation of myeloid progenitors and impaired hematopoiesis. Gene fusions involving KAT6A or KAT6B histone acetyltransferases occur in 6.5% of AMLs of the monocytic and myelomonocytic subtype4, and patients with these translocations generally have poor prognosis5,6. In such leukaemias, most of the KAT6A or KAT6B genes are fused to either another histone acetyltransferase (CBP, p300) or one of the CBP adaptor genes (TIF2, NCOA3)7. Expression of these fusion proteins was shown to block myeloid differentiation of the normal blood progenitors, locking the cells in a highly proliferative undifferentiated state8. The molecular mechanism of how the fusion proteins induce this leukemic phenotype are currently not understood and would be key for the development of successful specific therapies.

The proposed project will involve the following main aims:

Generate and characterize novel mouse leukaemia models driven by the oncogenic histone acetyltransferases.

We will establish a set of advanced KAT6A/B-fusion mouse AML models by inducing the desired chromosomal translocation endogenously using simultaneous CRISPR/Cas9 targeting of the two genomic loci in mouse blood progenitor cells. We will then characterize the established cell lines using cytomorphological, immunological and transcriptomic approaches.

Investigate the molecular mechanisms underlying the development of leukaemia in the established leukemic models.

We will profile the genomic occupancy of the fusion oncoproteins and will analyze changes in gene expression patterns and genome architecture upon their depletion. To link these to the changes in histone acetylation patterns, we will perform chromatin immunoprecipitation for major histone acetylation products of the oncogenic enzymes. We will complement these data by mass spectrometry-based analysis of the proteins associated with the fusions.

Explore specific vulnerabilities of the established leukemic cell lines in vitro and in vivo

To identify factors specifically required for the growth of the established mouse leukemic cells, we will perform CRISPR knockout pooled in vitro screens in these cells using sgRNA libraries targeting all the known chromatin-associated and druggable proteins. In addition, we will generate a custom CRISPR KO library against the genes specifically overexpressed in this leukaemia subtype as opposed to other mouse AML models and normal monocytes. We will validate the most promising hits by testing the effect of their depletion on leukemic cell proliferation in vitro and the onset of leukaemia upon transplantation into mouse recipients. This will be followed by investigating how the identified hits sustain the growth of the leukemic cells and how their function is linked to the KAT6A/B fusion proteins.

Literature references

[1] Meshorer, E. et al. Hyperdynamic plasticity of chromatin proteins in pluripotent embryonic stem cells. Dev Cell 10, 105-116 (2006). https://doi.org:10.1016/j.devcel.2005.10.017

[2] Flavahan, W. A., Gaskell, E. & Bernstein, B. E. Epigenetic plasticity and the hallmarks of cancer. Science 357 (2017). https://doi.org:10.1126/science.aal2380

[3] Sheikh, B. N. & Akhtar, A. The many lives of KATs - detectors, integrators and modulators of the cellular environment. Nat Rev Genet 20, 7-23 (2019). https://doi.org:10.1038/s41576-018-0072-4

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[5] Gervais, C. et al. Acute myeloid leukaemia with 8p11 (MYST3) rearrangement: an integrated cytologic, cytogenetic and molecular study by the groupe francophone de cytogenetique hematologique. Leukemia 22, 1567-1575 (2008). https://doi.org:10.1038/leu.2008.128

[6] Murati, A. et al. Genome profiling of acute myelomonocytic leukemia: alteration of the MYB locus in MYST3-linked cases. Leukemia 23, 85-94 (2009). https://doi.org:10.1038/leu.2008.257

[7] Wiesel-Motiuk, N. & Assaraf, Y. G. The key roles of the lysine acetyltransferases KAT6A and KAT6B in physiology and pathology. Drug Resist Updat 53, 100729 (2020). https://doi.org:10.1016/j.drup.2020.100729
[8] Huntly, B. J. et al. MOZ-TIF2, but not BCR-ABL, confers properties of leukemic stem cells to committed murine hematopoietic progenitors. Cancer Cell 6, 587-596 (2004). https://doi.org:10.1016/j.ccr.2004.10.015

Candidate profile

Note: the ICR's standard minimum entry requirement is a relevant undergraduate Honours degree (First or 2:1).

Pre-requisite qualifications of applicants: Undergraduate Honours degree (First or 2:1).

Intended learning outcomes:

- Expertise in a range of molecular and cell biology, biochemistry and genomics approaches
- Excellent understanding of chromatin regulation and cancer biology
- Project management skills
- Oral and written scientific communication skills

Advertising details

Project suitable for a student with a background in:

- [x] Biological Sciences
- [ ] Physics or Engineering
- [ ] Chemistry
- [ ] Maths, Statistics or Epidemiology
- [ ] Computer Science