Investigation of the role of HLTF loss in Acute Myeloid Leukemia pathogenesis

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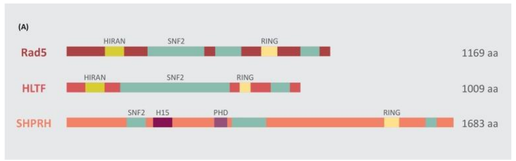
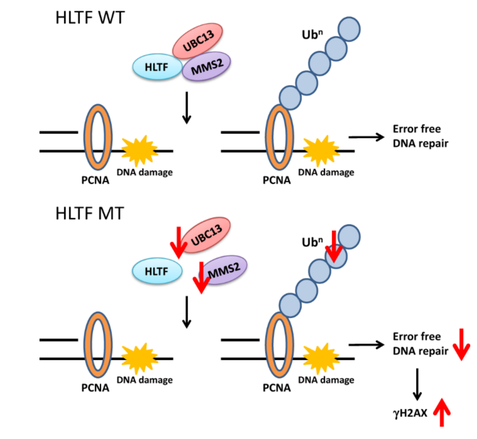
Introduction

1. *HLTF* is a SWI/SNF family member and a homologue of the yeast DNA repair gene, *Rad5*



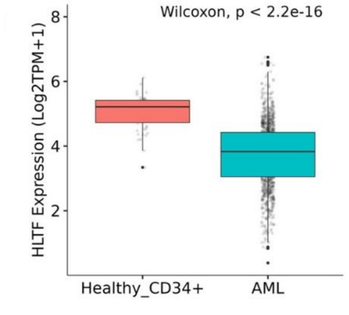
HLTF and SHPRH both conserve the RING domains, but only HLTF shares the HIRAN domain with Rad5 (Elserafy et.al. 2018)

2. HLTF is involved in post replication repair (PRR) via PCNA polyubiquitination



HLTF uses it's RING domain to act as an E3-Ligase (Takaoka et.al. 2019)

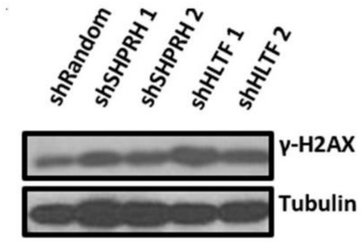
2. HLTF expression is downregulated in AML patients compared to healthy CD34+ samples



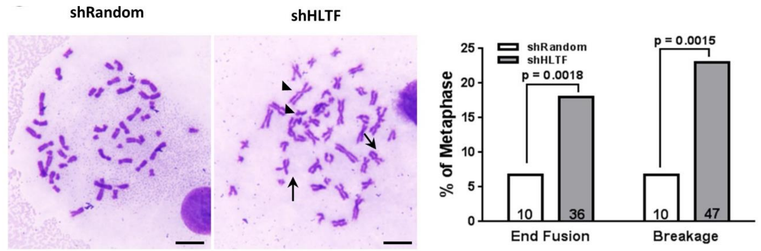
AML patient : n=1074, TCGA, PMP, Beat and Leucegene.
Healthy samples: n=55, Blueprint, Boultwood, Leucegene.

Results

1. HLTF KD cells exhibit increased double-stranded breaks (DSBs) and chromosomal translocations

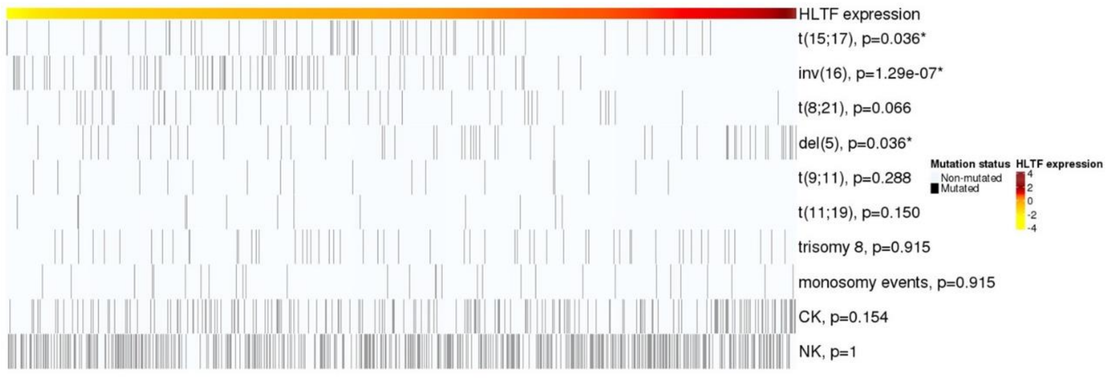


HLTF KD UT-7 cells show increased gamma-H2AX signal



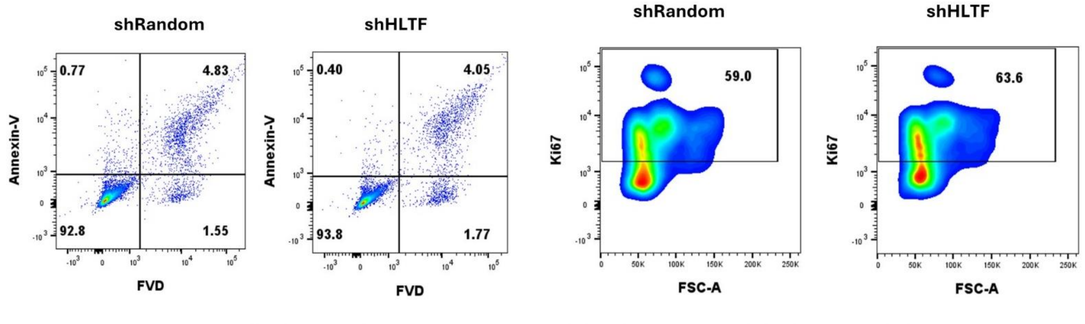
HLTF KD KG1a cells show increased chromosomal breakages and end-to-end fusions

2. Chromosomal translocations, t(15;17) and inv(16) show association with HLTF loss in AML



Oncoprint arranged as per HLTF expression (n = 1074 de novo AML patients)

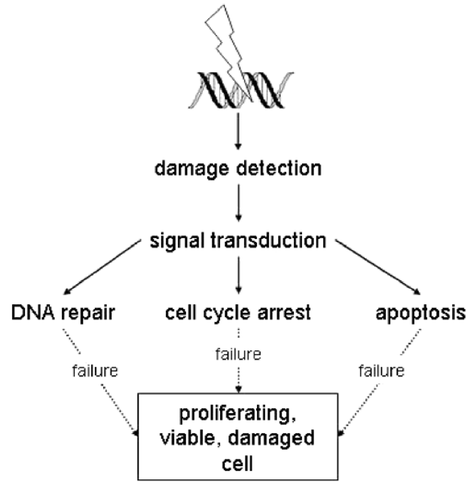
3. Despite inducing significant genomic instability, HLTF loss does not induce the cellular responses to DNA damage – apoptosis and cell cycle arrest



HLTF KD OCI-AML3 cells show no change in Annexin-V/Viability dye staining while showing a slight increase in Ki67 expression

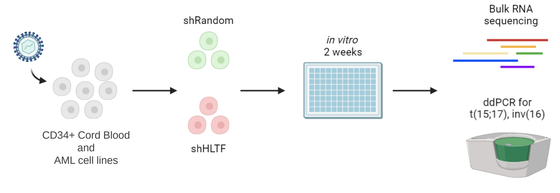
Conclusion

The simultaenous effects of DNA damage and mitigation of DNA-damage combative cellular responses could potentially lead to oncogenesis or over time (Norbury et.al. 2004)



Future Directions

We hypothesize HLTF loss leads to t(15;17) and inv(16) AML. We plan to experimentally induce and detect these fusions transcripts.



Acknowledgements

BC CANCER
CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada
UBC
Genome British Columbia
Leading • Investing • Connecting