The BLM helicase enables Alternative Lengthening of Telomeres to allow cancer cells to achieve telomerase-independent cellular immortality

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Introduction

- Telomeres protect chromosome ends from the DNA damage response
- 10-15% of cancer cells can maintain telomere independently of telomerase, via Alternative Lengthening of Telomeres (ALT)
- ALT is initiated by DNA damage at the telomere
- Enables cells to escape replicative senescence
- ALT is prevalent in mesenchymal and other intractable cancers, including breast, pancreatic, and hematologic
- The BLM helicase is crucial for ALT, first discovered in the cancer predisposition condition Bloom's syndrome
- BLM is part of the BTR (BLM-RMI1/2-TOP3A complex)

Methods

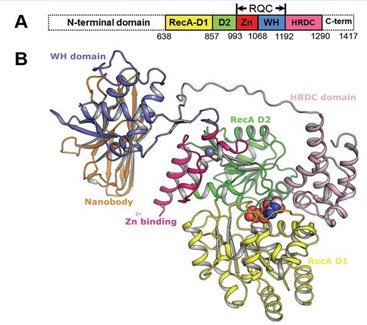

Figure 1: Structural domains of BLM[1]

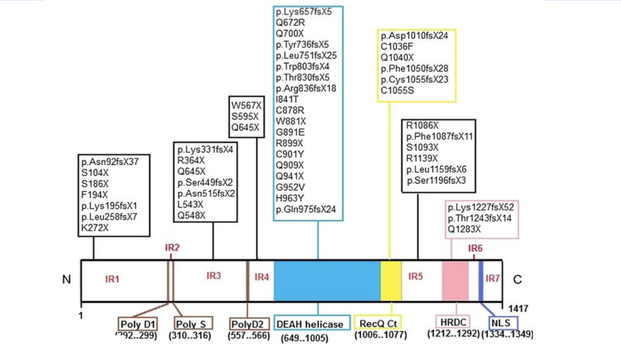

Figure 2: Patient mutations in BLM seen clinically[2]

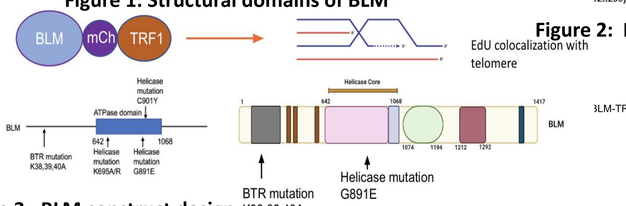

Figure 3: BLM construct design

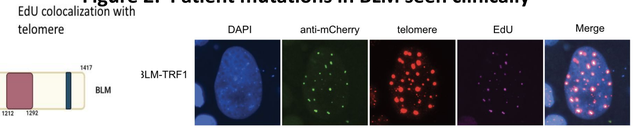

Figure 4: IF-FISH fluorescence microscopy for in vivo imaging

Discussion

- BLM is an upstream mediator of ALT, causing BLM-dependent ALT features like telomere clustering
- DNA synthesis at the telomere is dependent on cells having helicase-functional BLM, regardless of other BTR complex components
- The helicase activity of BLM is essential for promoting telomere extension via ALT
- ALT, driven by BLM, is determined by the tightness of chromatin packing, based on expression of ATRX
- BLM recruitment to telomeres in ALT may occur through a similar process as at stalled replication forks

Conclusions

- BLM's helicase domain is a promising target to modulate for ALT-dependent cancers
- BLM is specifically essential for lagging strand synthesis at the telomere, and may be genome-wide
- Further studies are needed to determine how BLM is recruited to telomeres for ALT

Results

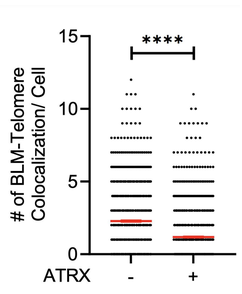

Figure 5: BLM localization to telomeres is impacted by ATRX (regulator of chromatin packing)

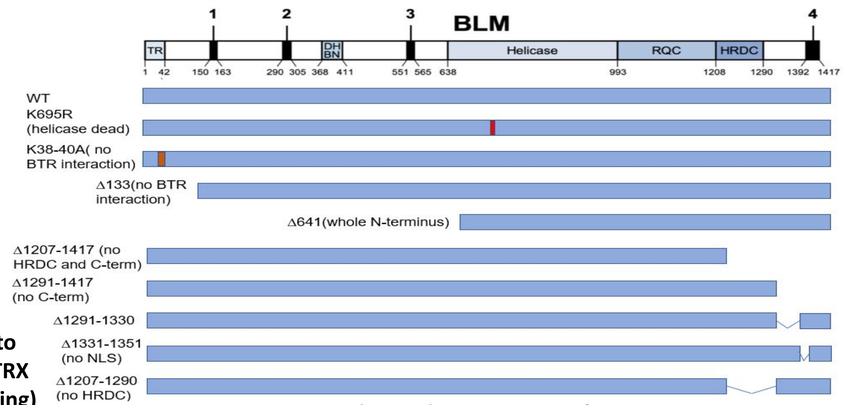

Figure 6: Site-directed mutagenesis of BLM

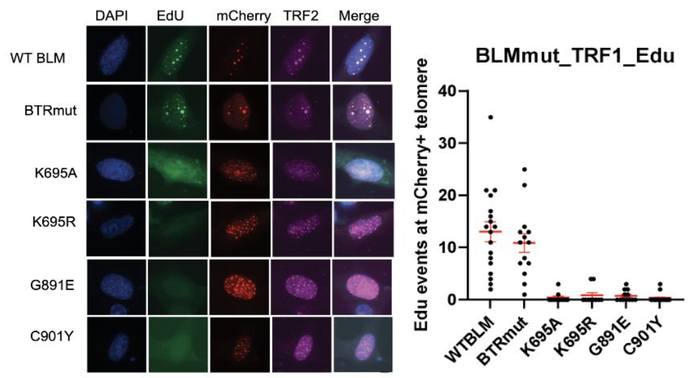

Figure 7: BLM helicase activity is required to drive telomere synthesis via ALT

Figure 8: Hypothesized model for BLM recruitment to telomeres in ALT

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References

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