xCT expression alters the epigenome and induces genomic instability

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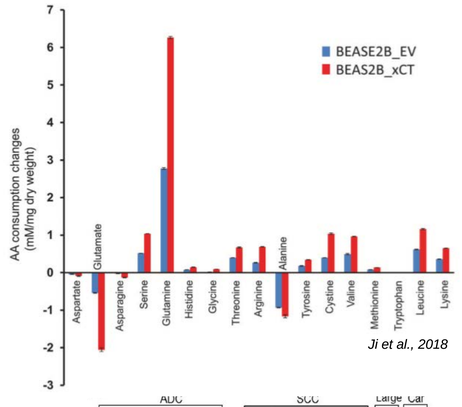
Background

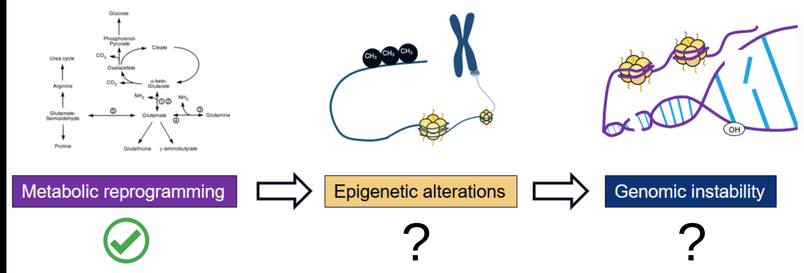
What we know:

- Genomic instability and metabolic reprogramming are two hallmarks of tumorigenesis
- The cystine-glutamate antiporter xCT is highly expressed in multiple lung cancer subtypes
- xCT overexpression induces metabolic reprogramming



What we don't know:

- How high xCT expression-induced metabolic reprogramming can promote genomic instability during tumorigenesis
- The influence of xCT-induced metabolic reprogramming on the epigenome and genomic instability during tumorigenesis



Aims

1. Identify the effects xCT expression has on gene expression

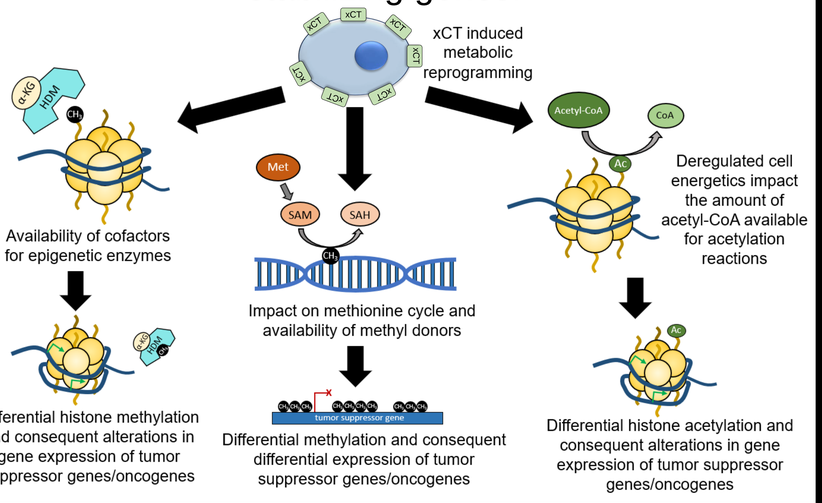
2. Investigate the impact of xCT overexpression on genomic instability

3. Explore the epigenetic changes induced by xCT overexpression

4. Elucidate causal links between xCT overexpression, epigenetic changes, and genomic instability

Hypothesis

We hypothesize that **xCT-induced metabolic reprogramming** influences **genomic instability** through altering the availability of **epigenetic-linked metabolites**, thus remodeling the epigenome and the expression of key genome stabilizing genes.



Results

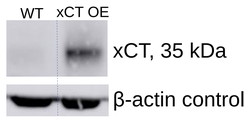
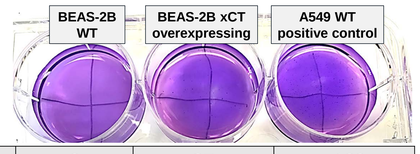


Figure 1. Western blot confirming our BEAS-2B xCT overexpressing cell line

Figure 2. A soft agar assay demonstrating the mild tumorigenic potential of BEAS-2B xCT overexpressing cells



Number of colonies	0	37	>100

BEAS-2B xCT Overexpressing

Upregulated	Downregulated
TNFAIP3	*PALMD*
CCND1	Collagen and ECM organization pathways
PI3K-Akt signaling	

Table 1. RNA Seq demonstrating key upregulated (logFC > 2.0, pAdj < 0.05) and downregulated transcripts (logFC < 0.50, pAdj < 0.05) and gene sets in BEAS2B xCT overexpressing cells compared to WT

Results

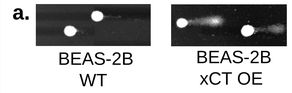
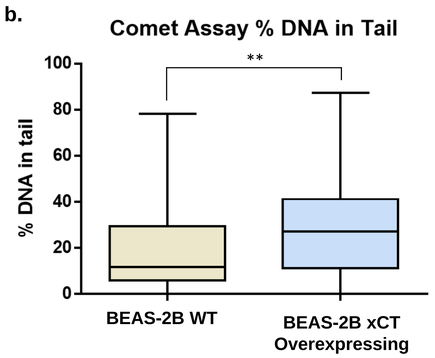


Figure 3a. Examples of single-cell comets from the alkaline comet assay **b.** The percentage of DNA in the tail of individual comets for BEAS-2B WT (n=101) and xCT overexpressing cells (n=60).



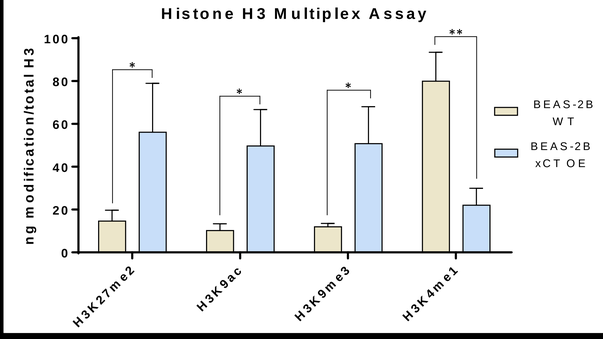


Figure 4. xCT overexpression results in an increase in several histone H3 modifications

Conclusions

xCT overexpression in normal bronchial airway epithelial cells:

- increases tumorigenic potential
- alters the expression of genes known to induce genomic instability
- induces DNA damage
- alters the histone modification landscape

Future Directions

- Perform ChIP-Seq and WGBS to connect dysregulated epigenetic modifications to altered gene expression
- Test panel of epigenetic enzyme inhibitors to identify any rescue of genome stability

Acknowledgements

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