**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.

**Figure 3a.** Examples of single-cell comets from the alkaline comet assay. **Figure 3b.** 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.

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