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Deciphering Hypoxia's Ally in Esophageal Cancer: Axin1 Lactylation as a Gateway to Glycolytic Mastery and Tumor Control

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Introduction

Background:

- Hypoxia is a critical factor in the progression of esophageal carcinoma, promoting tumor growth and resistance to therapy.
- Glycolysis is significantly enhanced under hypoxic conditions, leading to increased glucose intake, lactate production, and metabolic enzyme activity.
- Axin1, a multifunctional framework protein, plays a role in energy metabolism and has been linked to tumor progression.

Aim:

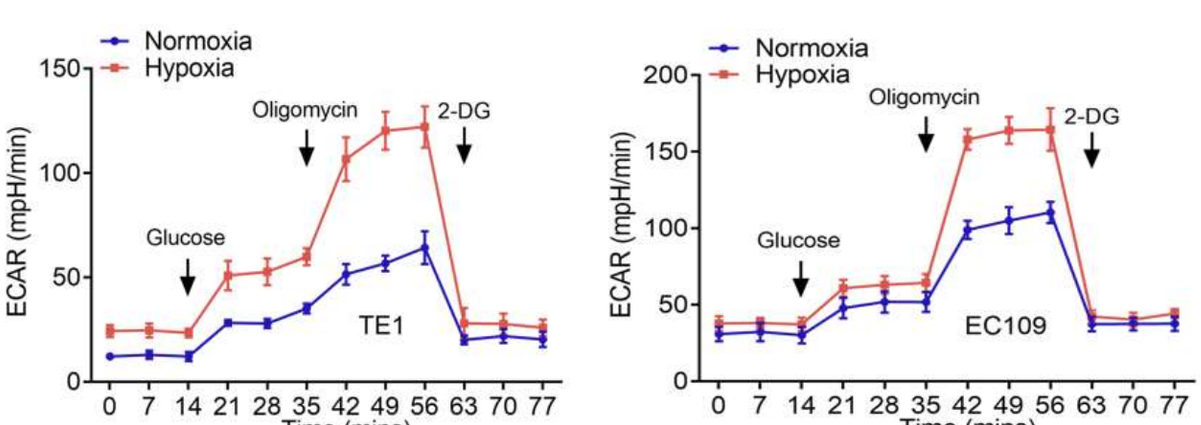
- To investigate how hypoxia-induced lactylation of Axin1 affects glycolysis and cell stemness in esophageal carcinoma cells.

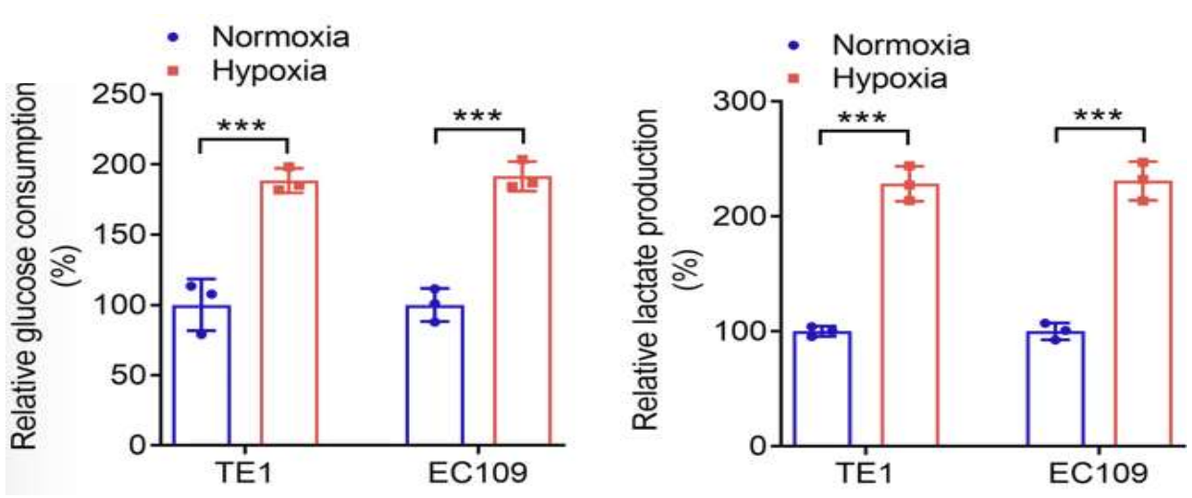
Materials and Methods

- Cell Lines: TE1 and EC109 human esophageal carcinoma cells.
- Hypoxia Treatment: Cells were cultured in 2% O2 for 24 hours.
- Western blotting for protein lactylation and ubiquitination.
- Seahorse analysis for extracellular acidification rate (ECAR).
- Glucose consumption and lactate production measured with commercial kits.
- Sphere formation assay for cancer stem cell detection.
- Mutation analysis using DeepKla online database.
- In vivo tumor xenograft studies in nude mice.

Results

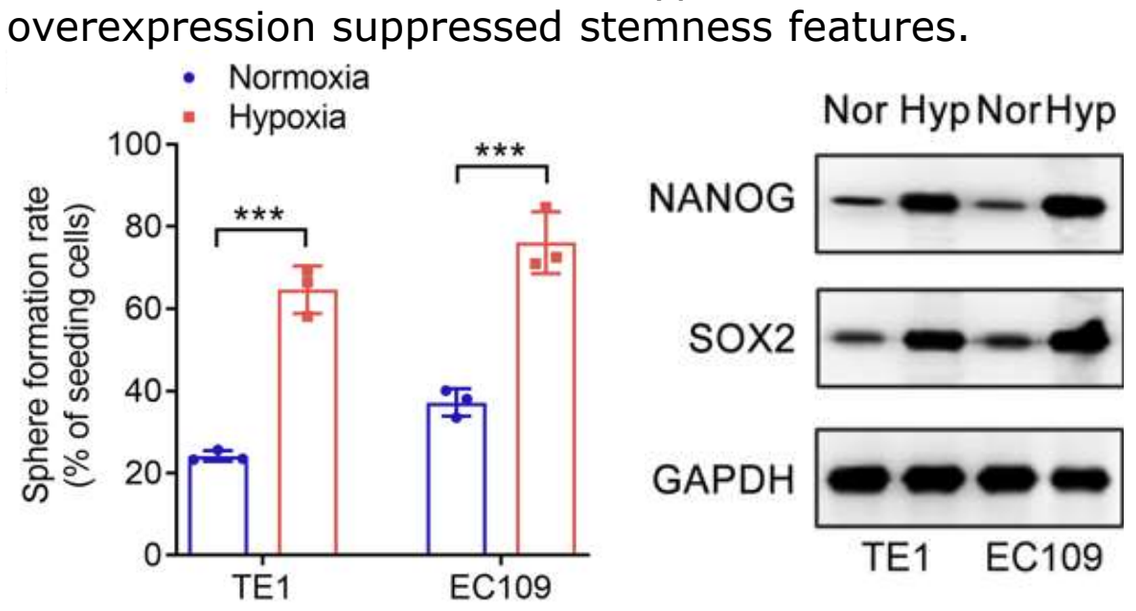
1. Hypoxia significantly increased pan lysine lactylation in TE1 and EC109 cells. Axin1 overexpression reduced hypoxia-induced lactylation and ubiquitination





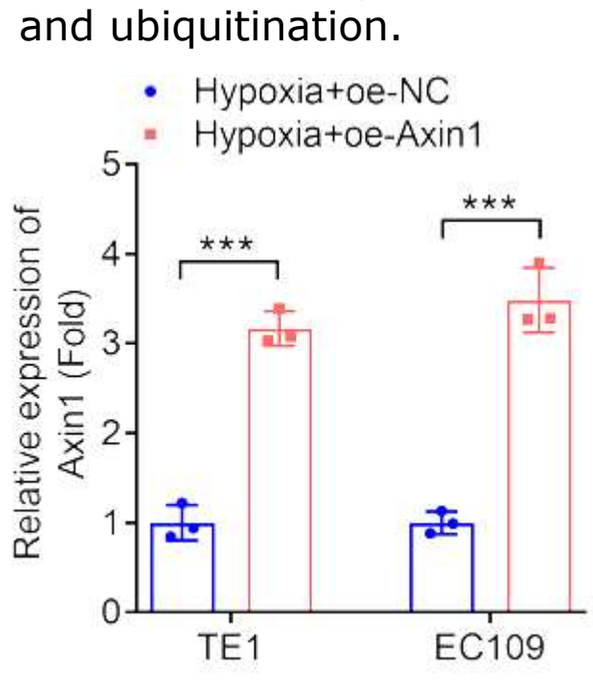
ECAR, glucose consumption, and lactate production in hypoxic conditions.

2. Sphere formation and expression of stem cell markers were elevated under hypoxia. Axin1 overexpression suppressed stemness features.

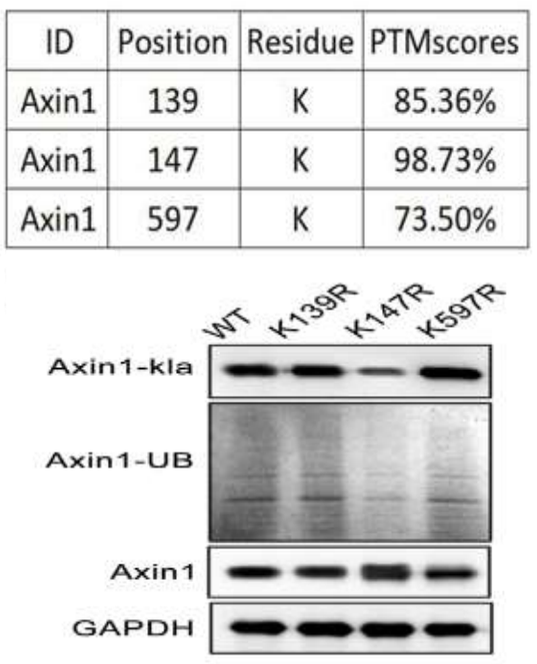


Sphere formation assay results under hypoxia.
Western blot analysis of NANOG and SOX2 expression.

3. Mutation analysis and its effects on lactylation and ubiquitination.

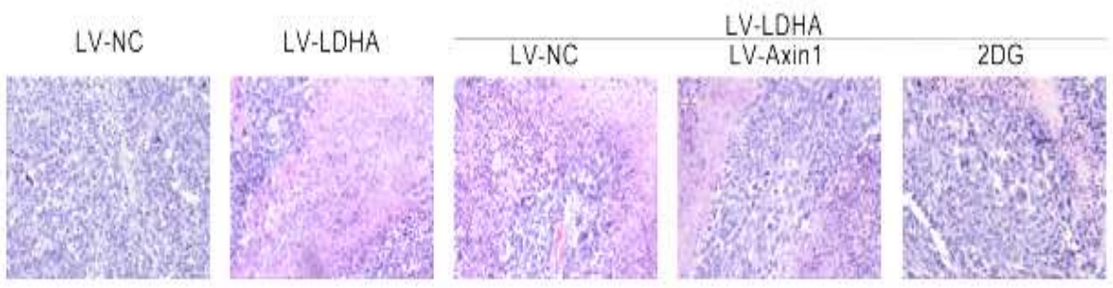


ID	Position	Residue	PTMscores
Axin1	139	K	85.36%
Axin1	147	K	98.73%
Axin1	597	K	73.50%



Effects of Axin1 overexpression on glycolysis markers.
Mutation analysis and its effects on lactylation and ubiquitination.

4. Axin1 overexpression inhibited tumor growth and glycolysis in xenograft models.



In vivo tumor growth and glycolysis inhibition by Axin1.

Discussion

Hypoxia is a crucial feature of tumor microenvironments, including esophageal carcinoma, driving metabolic adaptations that support tumor progression. This study focuses on the role of hypoxia-induced lactylation of the Axin1 protein in enhancing glycolysis and cell stemness in esophageal carcinoma cells.

Conclusion

Hypoxia promotes glycolysis and cell stemness in esophageal carcinoma by inducing lactylation of Axin1 at K147, leading to its degradation. Overexpression of Axin1 inhibits these effects, highlighting its potential as a therapeutic target.