

An Inhalational Stress Program Identifies a p53-High G1-Arrested Subpopulation With Glycolytic Features in EGFR-Mutant Lung Cancer

P. Chen, L. Shen, Y. Jiang, J. He, W. Liang

The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China

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BACKGROUND

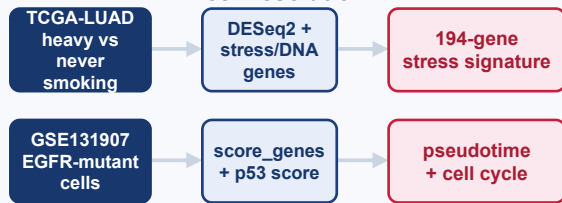
Environmental inhalational exposures may contribute to EGFR-TKI tolerance, but direct exposure data are often unavailable in public lung cancer cohorts.

OBJECTIVE

To define a transcriptomic inhalational stress program and determine its relationship with cell-cycle heterogeneity, p53-mediated arrest, and metabolic reprogramming in EGFR-mutant lung cancer.

STUDY DESIGN

Smoking-derived proxy signature applied to EGFR-mutant malignant epithelial cells at single-cell resolution.



Arrested G1; p53 score >0.2 in G1; Cycling control: p53 <=0.2 in S/G2M.

KEY RESULTS

Cell-cycle-dependent stress and p53 heterogeneity revealed a distinct p53-high G1-arrested cell state.

4,763

G1-phase cells

1,485

S-phase cells

1,304

G2/M-phase cells

7,552 EGFR-mutant malignant epithelial cells; inhalational stress score and p53 activity both differed by cell-cycle phase (Kruskal-Wallis $P < 0.001$).

TRAJECTORY AND ARRESTED STATE

$\rho = -0.09$

Stress score
vs pseudotime

$\rho = -0.31$

p53 score
vs pseudotime

314

Genes upregulated
in Arrested G1

Highly stressed and p53-high cells were preferentially concentrated toward earlier trajectory states, supporting a non-linear stress-selection pattern.

993

Arrested G1
subpopulation

2,207

Cycling
control cells

REPRESENTATIVE UPREGULATED GENES

Arrested G1 versus Cycling Control identified stress-response, stemness-associated and glycolytic features.

Gene	log2FC	Biological signal
GADD45A	2.84	DNA damage / p53 stress
CD44	1.27	Stemness-associated adhesion
SLC2A3	1.52	Glucose transport
HK2	1.17	Glycolysis

INTERPRETATION

- CD44 and GADD45A localized to the same high-stress subpopulation.
- SLC2A3 and HK2 enrichment indicates glycolytic reprogramming.
- Findings are hypothesis-generating and require experimental validation.

KEY TAKEAWAY

Inhalational stress marks a p53-high G1-arrested, CD44-positive and glycolytic persister-like state in EGFR-mutant NSCLC.