肺癌硼中子捕獲治療之精準醫學

Precision Medicine-Enabled Boron Neutron Capture Therapy (BNCT) for Lung Cancer

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Squamous cell carcinomas of the upper aerodigestive tract are highly lethal and share similar genetic alterations. Moreover, the lack of druggable targets and approved targeted therapies in these cancers has imposed challenges in patient treatment. Although BNCT has achieved a good response rate in head and neck squamous cell carcinomas, the resistance and tumor recurrence toward BNCT have rarely be studied. The solute carrier family 7 member 5 (SLC7A5) is a transporter responsible for uptake of large and neutral amino acid and serves as a potential carrier of p-boronophenylalanine (BPA) in boron neutron capture therapy (BNCT). Nonetheless, the role of SLC7A5 as a therapeutic target and biomarker in lung squamous cell carcinoma has yet to be examined. In the present study, we report that *SLC7A5* is highly expressed in squamous cell carcinomas of the upper aerodigestive tract, and its high expression predicts a poor survival outcome in patients with lung squamous cell carcinoma. Correlation analysis showed that *SLC7A5* expression was associated with *SOX2*, a cell fate determining gene of fast-growing lung squamous cell carcinoma. Knockdown of *SLC7A5* attenuated the ability of proliferation and decreased *SOX2* expression while inducing $p21^{CIP1}$ expression in lung squamous cell carcinoma cells. We have previously showed that the switch from SOX2-mediated pathway to TGF-β signaling contributes to cancer cell heterogeneity, generating resistance to epidermal growth factor receptor tyrosine kinase inhibitors [1,2]. Here, we discovered that knockout of *SLC7A5* caused the loss of *SOX2* expression with concomitant decrease of S phase cell cycle entry, whereas gaining epithelial to mesenchymal transition feature with activated TGF-β signaling in cancer cells. *SLC7A5* knockout blocked BPA uptake in lung squamous cell carcinoma cells, demonstrating the critical role of SLC7A5 in the transport of BPA. Treatment of lung squamous cell carcinoma cells with BNCT or chemotherapeutic agent cisplatin selected resistant cells with low *SLC7A5* expression. Our findings indicate the potential usage of *SLC7A5* as a therapeutic target and biomarker in lung squamous cell carcinomas. These data revealed for the first time that *SLC7A5* is essential in fast-growing lung squamous cell carcinoma, and the decreased expression of *SLC7A5* may contribute to drug resistance to BNCT and chemotherapy.

References

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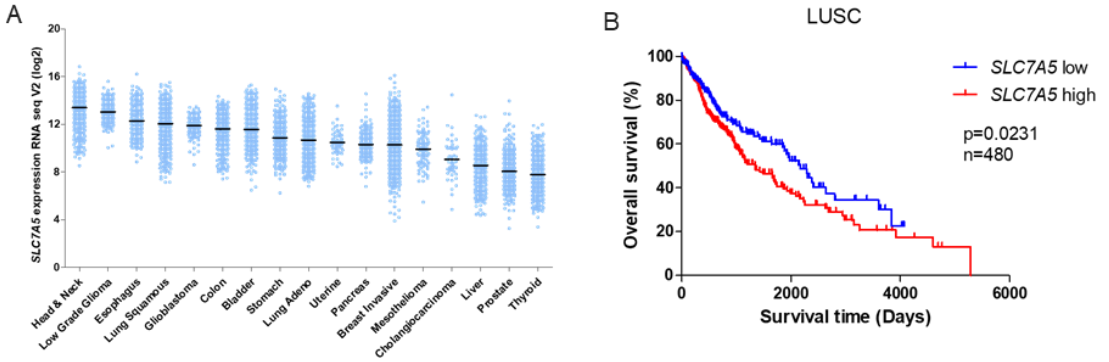

Figure 1. *SLC7A5* as a prognosis marker. (A) Gene expression profiling analysis to assess *SLC7A5* expression in different cancers obtained from TCGA datasets. (B) Kaplan-Meier analysis to correlate *SLC7A5* expression with the overall survival in patients with lung squamous cell carcinoma TCGA_LUSC cohort.

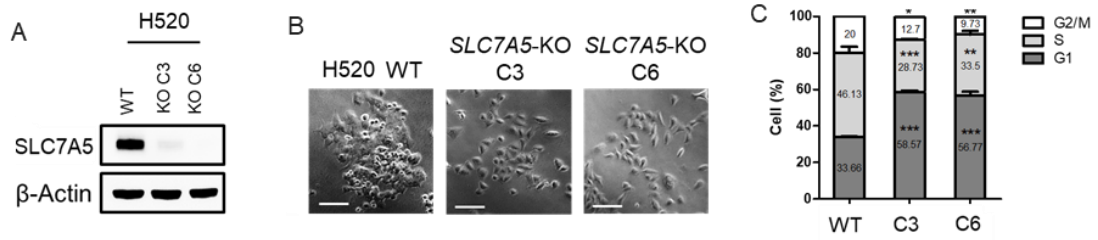

Figure 2. SLC7A5 knockout lung cancer cells exhibit morphological changes and deceased cell proliferation. (A) Immunoblotting to assess SLC7A5 expression in H520 wild-type and SLC7A5 knockout cells. (B) Phase-contrast imaging analysis of H520 wild-type and SLC7A5 knockout cells. (C) Cell cycle analysis of H520 wild-type and SLC7A5 knockout cells.

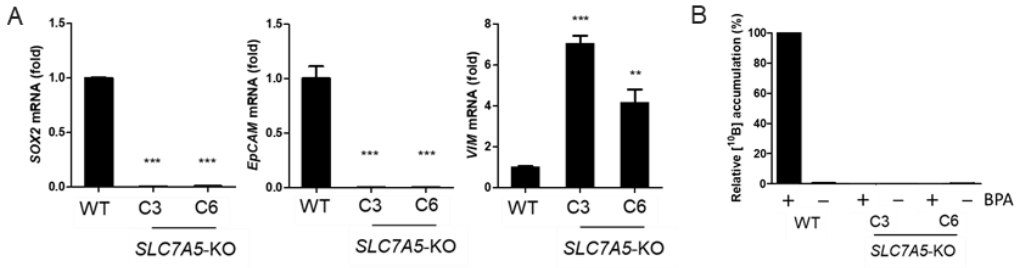

Figure 3. Knockout of SLC7A5 blocks BPA uptake and generates epithelial-to-mesenchymal transition feature with deficient SOX2 expression in lung squamous cell carcinoma. (A) Q-PCR analysis to assess SOX2, EpCAM, and VIM expression in H520 wild-type and SLC7A5 knockout cells. (B) ICP-mass analysis to assess 10B accumulation in H520 wild-type and SLC7A5 knockout cells. Cells were treated with 10B-BPA-fructose (25 ppm) for 24 hr.

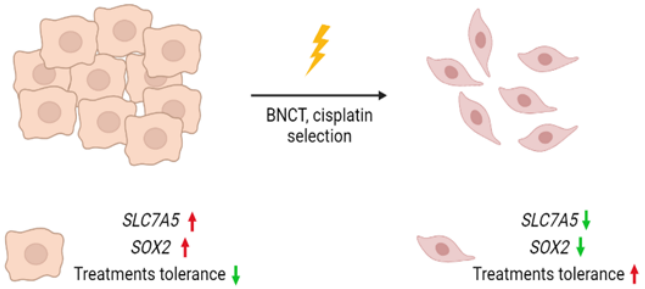

Figure 4. Model of the crosstalk between *SLC7A5* and *SOX2* proliferation signaling in lung squamous cell carcinoma. *SOX2* signaling promotes proliferation but inhibits epithelial-to-mesenchymal (EMT) transition in lung squamous cell carcinoma. *SOX2*-positive high-proliferative lung squamous cell carcinomas exhibit higher demands for SLC7A5-mediated uptake of essential amino acids, such as phenylalanine. BPA-BNCT or chemotherapy select resistant cancer cells with lower SLC7A5 expression, causing the enrichment of low-proliferative cancer cells, which exhibit EMT and deficient *SOX2* expression