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Thioredoxin reductases 1: A key member in metabolism newly identified as prognostic and targetable in non-small cell lung cancer (NSCLC)

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Background: Deregulating cellular energetics is one promising hallmark of cancer. Thioredoxin reductases 1 (TrxR 1), a member of the family of selenium-containing pyridine nucleotide-disulphideoxidoreductases, plays a key role in cell metabolism. Over expression of TrxR1 was observed in many malignancy diseases and commonly considered as poor prognostic factor, yet the role of TrxR1 remained unclear in NSCLC.

Aim: To identify the prognotic role and signaling of TrxR1 in NSCLC.

Methods: In cohort one, TrxR1 level in carcinoma tissues and para-carcinoma tissues of 50 resected NSCLC patients were evaluated by immunohistochemistry. In cohort two, serum level of TrxR1 in 60 metastatic EGFR wide type NSCLC patients was measured by ELISA assay before receiving first line standard doublet chemotherapy. Patients of the two cohorts were from database NCT01980212 and NCT01991418. Survivor data were collected and analyzed according to TrxR1 levels. Experiments in vitro were performed to explore TrxR1 signaling in NSCLC.

Results: TrxR1 level was higher in cancer tissues compared to surrounding normal tissues in approximately 50% patients in cohort 1. Survivor data analysis in cohort 2 showed that the lower TrxR1 activity group was with significantly longer PFS compared to the higher in the total (4.0 m vs. 2.5 m, p=0.00001), adeno subtype (5.0 m vs. 2.2 m, p=0.009) and squamous subtype (3.8 m vs. 2.1 m, p=0.016). In vitro study, it was observed that TxrR1 inhibited cell apoptosis through up-regulating the expression of NF-kB p65 in A549 cell line and BBSKE (a novel organoselenium anticancer drug under development) inhibited TrxR1 by down regulating p65.

Conclusions: Over expression of TrxR1 could be an important signature for NSCLC, which may suggest poor prognosis for EGFR wild type NSCLC patients treated with chemotherapy regardless of histology type and possibly those patients would be compliant to therapy targeting TrxR1 pathway. Further preclinical and clinical studies are warranted to profile TrxR1 inhibitors from bench to bedside.

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