Prognostic and predictive effects of a gene expression signature for NRF2 pathway activation in lung squamous cell carcinoma (SqCC).

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Background: Genomic profiling of SqCC in TCGA identified somatic alterations that activate the NRF2 transcriptional program – a master regulator of the oxidative stress response – in ~35% of tumors (NFE2L2 mutations/amplifications, KEAP1 or CUL3 mutations/deletions). This pathway has been implicated in resistance to chemotherapy. To evaluate the clinical significance of this molecular subset, we developed a gene expression classifier and tested this signature as a predictor of adjuvant chemotherapy benefit with cisplatin/vinorelbine (cis/vin) in a subset of SqCC patients with microarray data from the NCIC JBR.10 Phase III clinical trial. **Methods:** Logistic regression (LR) and SAM analysis were independently applied to 104 TCGA SqCC cases that had both microarray gene expression and mutation data to identify genes associated with NRF2 pathway mutational status. Overlapping genes were used to define the signature, which was then tested in 3 independent SqCC datasets (62 JBR.10; 54 UHN; 129 UM) to evaluate the prognostic and predictive values of putative NRF2 pathway activation. **Results:** 29 genes comprising the signature were identified by overlap between LR (291 genes) and SAM (45 genes). The signature consistently separated SqCC into 2 groups in all datasets, corresponding to putatively activated and wild type (WT) NRF2 pathway tumors. No prognostic effect of the activated signature was observed in independent datasets (UHN HR 0.86, 95%CI 0.28 – 2.67; UM HR 1.43, 95%CI 0.82 – 2.48). Similarly, in JBR10, no prognostic effect was observed in the observation arm (n=24, HR 0.66, 95%CI 0.13 – 3.29). A trend toward improved survival with adjuvant chemotherapy was observed in patients with the WT signature (HR 0.34, 95%CI 0.08 – 1.78, p=0.13), but not in patients with the activated signature (HR 1.16, 95%CI 0.19 – 6.97, p=0.87; interaction p=0.18). **Conclusions:** A gene expression signature based on mutational activation of the NRF2 pathway may be predictive of benefit from adjuvant cis/vin in SqCC. Patients with NRF2 pathway activating somatic alterations may have reduced benefit from this therapy. Validation of this potentially "actionable" finding in additional datasets is necessary.