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prognostic markers in Asian oral squamous cell
carcinoma

Hui-Ching Wang^{1,2}, Chien-Jung Chiang³,
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Abstract

High mortality is associated with oral squamous cell carcinoma (OSCC), and little improvement has been made in the 5-year survival rate of patients over the years. Obtainment of tumor tissues for cytopathology or histopathology is still the main strategy for diagnosis and the following management of this disease. Here, we aim to uncover individual and paired IHC prognostic markers in Asian OSCC. Two genes are called synthetic lethal if a single mutation of either is not lethal, but their simultaneous mutation leads to cell death. From the validated 742 synthetic lethal (SL) gene pairs, we first sifted relevant ones by gene expression of Asian OSCC tumor and non-cancerous tissues. Next, 21 genes were selected from top-ranked co-expressed relevant SL pairs for *immunohistochemistry* (IHC) staining at different cellular locations. We combined the 29 individual IHC into 398 distinct pairs, which enabled novel paired IHC markers revealed. *Increased immunohistochemical expression* of RB1 (FLNA) in cytoplasm RB1(C) ↑ (FLNA(C) ↑) was shown to be significantly associated with poor (good) overall survival of 153 OSCC patients in Taiwan (P-value = 0.027 (0.047); log-rank test). Of all IHC pairs, FLNA(C) ↑ -SHC1(N) ↓, FLNA(C) ↑ -KRAS(C) ↑, POLB(N) ↓ -SGK2(C) ↑, CSNK1E(C) ↓ -SHC1(N) ↓, CSNK1E(C) ↓ -RB1(C) ↑, CDH3(C) ↑ -STK17A(N) ↑, BRCA1(N) ↓ -SHC1(N) ↓ and SHC1(N) ↓ -TP53(N) ↑ were significantly associated with patients' overall survival (p-value < 0.05; log-rank test). Importantly, multivariate Cox regression analyses unraveled that CSNK1E(C) ↓ -SHC1(N) ↓ [hazard ratio (95% confidence interval) = 7.75 (2.85-21.07); P-value = 5.9×10^{-5}], CSNK1E(C) ↓ -RB1(C) ↑ [hazard ratio (95% confidence interval) = 2.16 (1.02-4.58); P-value = 0.045] and BRCA1(N) ↓ -SHC1(N) ↓ [hazard ratio (95% confidence interval) = 2.87 (1.11-7.42); P-value = 0.030] were significant predictors for risk of death, independent from age, stage and the carcinogen alcohol. Finally, an external dataset (160 HPV(-) OSCC tumors from the TCGA cohort, ~98.7% non-Asian) validated that CDH3 ↑ -STK17A ↑ and CSNK1E ↓ -RB1 ↑ were significant predictors for risk of death, where ↑ and ↓ denote over- and under-expression of the corresponding genes.