Functional Genomics Uncover the Biology behind the Responsiveness of Head and Neck Squamous Cell Cancer Patients to Cetuximab

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PURPOSE
To identify the tumor portrait of the minority of head and neck squamous cell carcinoma (HNSCC) patients with recurrent-metastatic (RM) disease who upon treatment with platinum-based chemotherapy plus cetuximab present a long-lasting response.

EXPERIMENTAL DESIGN
The gene expression of pretreatment samples from 40 HNSCC-RM patients, divided in two groups [14 long-progression-free survival (PFS) and 26 short-PFS (median = 19 and 3 months, respectively)], was associated with PFS and was challenged against a dataset from metastatic colon cancer patients treated with cetuximab. For biologic analysis, we performed functional and subtype association using gene set enrichment analysis, associated biology across all currently available HNSCC signatures, and inferred drug sensitivity using data from the Cancer Genomic Project.

RESULTS
The identified genomic profile exhibited a significant predictive value that was essentially confirmed in the single publicly available dataset of cetuximab-treated patients. The main divergence between long- and short-PFS groups was based on developmental/differentiation status. The long-PFS patients are characterized by basal subtype traits such as strong EGFR signaling phenotype and hypoxic differentiation, further validated by the significantly higher association with the hypoxia metagene. The short-PFS patients presented a strong activation of RAS signaling confirmed in an in vitro model of two isogenic HNSCC cell lines sensitive or resistant to cetuximab. The predicted drug sensitivity for all four EGFR inhibitors was higher in long- versus short-PFS patients (P range: <0.0022-1e-07).

CONCLUSIONS
Our data uncover the biology behind response to platinum-based chemotherapy plus cetuximab in RM-HNSCC cancer and may have translational

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