#6053

Comprehensive proteomic and genomic profiling to identify therapeutic targets in adenoid cystic carcinoma

Sheeno P. Thyparambil[1], Yeoun Jin Kim[1], Andrew G. Chambers[1], Dongyao Yan[1], Shankar Sellappan[1], Chao Gong[1], Andrew J. Sedgewick[2], Yulia Newton[2], J. Zachary Sanborn[2], Charles J. Vaske[2], Stephen C. Benz[2], Fabiola Cecchi[1], Hyunseok Kang[3], Todd A. Hembrough[1]

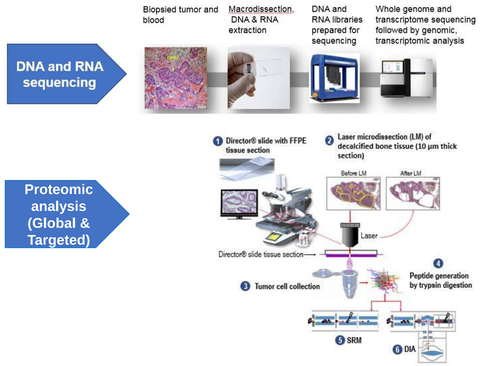
[1]NantOmics, Rockville, MD; [2]NantOmics, Santa Cruz, CA; [3]Johns Hopkins Medical Institutions, Baltimore, MD

BACKGROUND

- Adenoid cystic carcinoma (ACC) is rare cancer with an indolent clinical course. ACC does not typically respond to conventional systemic therapy. The 15-year survival rate is 40%.
- ACC has a low mutational rate and wide mutational diversity. ACC is characterized by mutations in chromatin remodeling genes and by *MYB-NFIB* and *MYBL1-NIFB* fusion.
- ACC has not been proteomically characterized.
- We performed proteogenomic analysis of ACC tumors to identify (1) clinically relevant molecular differences between ACC and other tumor types, (2) altered disease pathways, and (3) potential drug targets in ACC.

METHODS

- Clinical samples of ACC (n=7) and squamous cell carcinoma (SCC) of the head and neck (n=6) were subjected to whole genome/exome sequencing, RNA-seq and global proteomic analysis.
- Proteins that were overexpressed or underexpressed were subjected to pathway analysis to identify potential drug targets.
- mRNA expression in ACC and various solid tumor types were compared using the k-nearest neighbors algorithm.
- ACC clinical samples (n=28) were also subjected to targeted proteomic analysis of clinically actionable targets.



RESULTS

Proteogenomic characterization of ACC

ACC is proteomically distinct from SCC

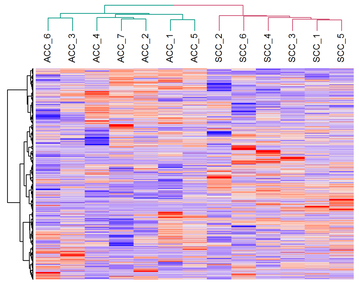


Figure 1. Unsupervised hierarchical cluster analysis of 3362 proteins distinguishes ACC from SCC.

Similarity of ACC to other cancer types

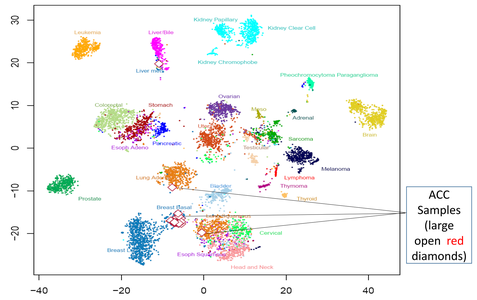


Figure 2. ACC is genomically similar to breast cancer: t-distributed stochastic neighbor embedding (t-SNE) of ACC to other types of cancer.

Genetic alterations in ACC

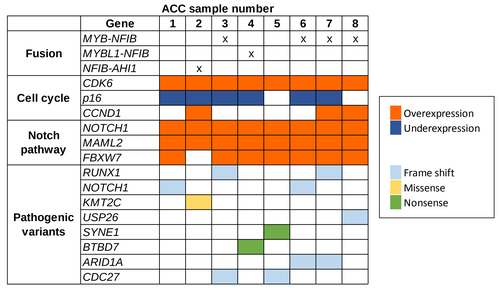
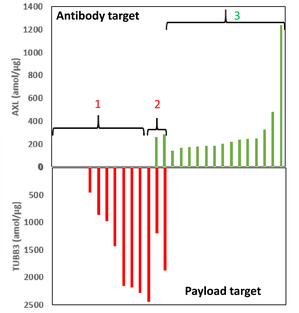


Figure 3. Data from WGS and RNA-seq reveal that ACC is characterized by fusions, perturbed Notch and cell cycle pathways, and pathogenic variants.

Distribution of Axl ADC targets in ACC



Potentially ineffective
1. No Axl receptor
2. Axl receptor present, however, resistance by TUBB3

Potentially Effective
3. Axl receptor present, without resistance by TUBB3

Figure 7. Combined targeted proteomic analysis of Axl and TUBB3 (marker for resistance of tubulin inhibitors) reveals that 50% of ACC might be sensitive to antibody-drug conjugates (ADC) that targets AXL with payload that disrupts tubulin.

CDK6 as a potential drug target in ACC

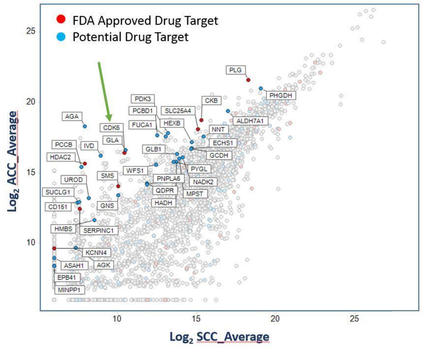


Figure 4. Protein levels (measured as area under the curve) in adenoid cystic carcinoma (ACC) vs. squamous cell carcinoma (SCC) reveal overexpression of several targetable proteins including CDK6.

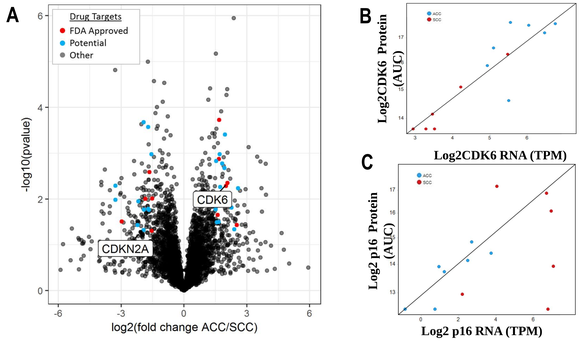


Figure 5. (A) Proteomically, CDK6 is overexpressed and p16 is underexpressed in ACC as compared with SCC. **(B, C)** RNA-seq (transcripts per million) vs protein levels show higher CDK6 levels and lower p16 levels in ACC. The three highest p16 levels were from HPV-positive patients with SCC.

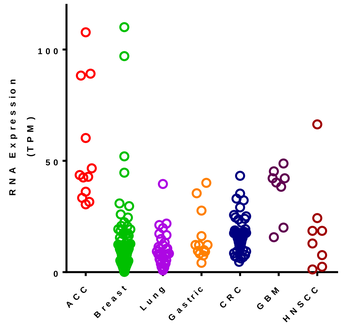


Figure 6. CDK6 RNA expression in multiple tumor samples. Expression in ACC is higher than in most cancer types.

CONCLUSIONS

- Proteogenomic analysis revealed CDK6 overexpression in ACC.
- The combination of CDK6 overexpression, p16 underexpression, and retinoblastoma (RB1) proficiency suggests that ACC tumors may respond to treatment with CDK6 inhibitors.
- ACC is molecularly more similar to breast cancer than to other cancer types.
- Targeted proteomics revealed that 50% of ACC might be sensitive to ADC that targets Axl with a payload that disrupts tubulin.