Poster ThP-679

Proteomic Quantitation of ERCC1 May Predict Response to Platinum-based Chemotherapy in Patients with Non-small Cell Lung Cancer

Chao Gong[1], Fabiola Cecchi[1], Eunkyung An[1], Jean-Charles Soria[2], Todd Hembrough[1]

1. Research & Development, NantOmics, Rockville, Maryland, USA. 2. Department of Drug Development, Gustave-Roussy Cancer Campus, Villejuif, France

Background

- Excision repair cross-complementing group 1 (ERCC1) protein plays a role in detection and repair of DNA damage. In cancer patients, tumor expression of ERCC1 is associated with resistance to platinum-based chemotherapy.[1, 2]
- The unreliability of ERCC1 assessment by immunohistochemistry (IHC) was attributed to the antibody and led to cancelation of the TASTE trial of biology-driven chemotherapy in lung cancer.[1, 2, 3]
- We developed a mass spectrometry (MS) based selected reaction monitoring (SRM) assay to quantitate ERCC1 level in formalin-fixed, paraffin-embedded (FFPE) tumor tissue.
- To assess the correlation between tumor expression of ERCC1 and patient response to platinum therapy, we applied the SRM assay to the archived tumor samples of non-small cell lung cancer (NSCLC) patients who received platinum during the TASTE trial.[3]

Methods

Sample Preparation and Analysis by SRM Assay

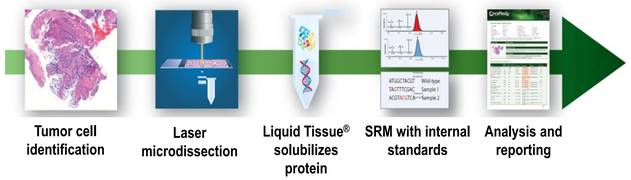

Figure 1. Laser microdissection and Liquid Tissue® SRM workflow to quantify protein biomarkers in FFPE tumor tissue

Multiplexed Clinical Proteomic Menu

Diagnostic protein markers: ALK, AR, AXL, MET, E-cadherin, EGFR, ERCC1, FGFR1, FGFR2, FGFR3, pan-FGFR, FR-alpha, GPNMB, hENT1, HER2, HER3, IDO1, IGF1R, KRAS, KRT5, KRT7, MGMT, MSLN, P16, PDL1, RET, RON, ROS1, RRM1, TLE3, TOPO1, TOPO2A, TP63, TROP2, TTF1, TUBB3, Vimentin

Quality control markers: Actin, Tubulin

Results

Quantitation by Peak Ratio of Analyte to Internal Standard

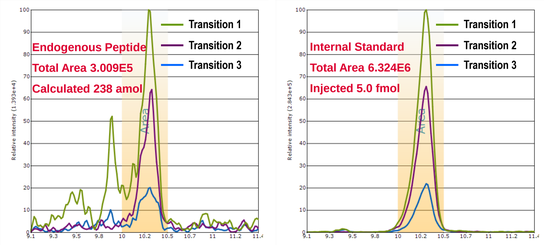

Figure 2. Representative spectra of endogenous ERCC1 peptide (left) and internal standard (right) in FFPE tumor tissue

Concentration Curve of ERCC1 Assay

Spiked ERCC1 peptide (amol)	Recovered ERCC1 peptide (amol)	CV (%) (n=5)	Accuracy (%)
50	55.4	6.6	110.8
75	74.8	3.6	99.7
100	100.9	5.6	100.9
300	273.7	3.2	91.2
500	462.0	4.6	92.4
1000	918.6	2.4	91.9
5000	4510.9	0.6	90.2
25000	22789.0	1.9	91.2

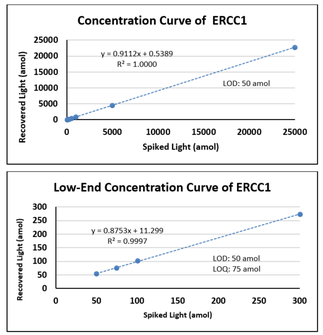

Figure 3. The amount of ERCC1 light peptide recovered (amol) in digest matrix was plotted against the amount of light peptide spiked (amol) to create a concentration curve.

Inter-Instrument Precision of ERCC1 Assay

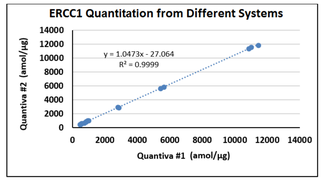

Figure 4. The amounts of quantified ERCC1 light peptide (amol) in liver matrix from LC-MS instrument #1 was compared to ERCC1 quantitations from LC-MS instrument #2.

ERCC1 Expression in Multiple Tumor Types

Metric	GRAND TOTAL (amol/µg)	STOMACH (amol/µg)	BREAST (amol/µg)	LUNG (amol/µg)	OTHER (amol/µg)
Minimum	75.2	75.2	75.5	75.9	78.0
10%	79.5	77.1	82.6	77.8	82.3
25%	87.2	82.3	96.2	82.6	92.0
50%	105.3	90.7	117.0	91.6	121.8
75%	135.7	110.1	143.7	115.0	210.9
90%	192.2	120.1	187.9	137.4	341.5
Maximum	525.0	169.1	352.6	203.6	525.0
Total tested (n)	920	259	255	236	170
Total positive (n)	252	34	110	59	49
Prevalence (%)	27.4%	13.1%	43.1%	25.0%	28.8%

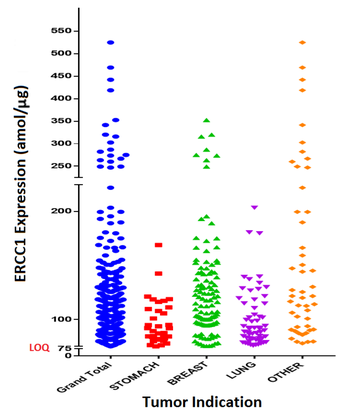

Figure 5. The SRM assay quantified a wide dynamic range of ERCC1 protein in various tumor types.

ERCC1 Status by MS and IHC

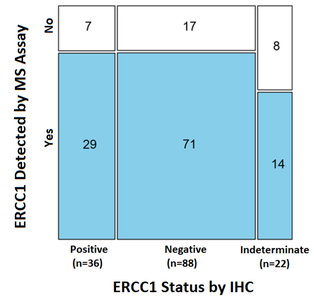

Figure 6. There was no association between proteomic ERCC1 levels and IHC status in NSCLC tumor samples (n=146). Proteomically detectable levels of ERCC1 were found in 71 of 88 (81%) IHC-negative patients.

Association between Proteomic ERCC1 and Survival

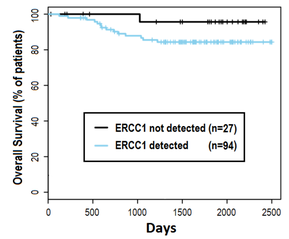

Figure 7. In survival analysis of platinum-treated NSCLC patients (n=121), there were 15 deaths. One death occurred among patients with non-detectable ERCC1 (n=27). In contrast, 14 of 94 (15%) patients with detectable ERCC1 died.

Conclusions

- An MS assay quantified a wide range of ERCC1 expression levels in various tumor types.
- The MS assay's sensitivity was superior to ERCC1 IHC in samples from 146 lung cancer patients.
- The MS assay retrospectively identified responders to platinum and could potentially be used to select cancer patients for personalized treatment with platinum-based chemotherapy.

References

1. Wislez et al. 2014. J. Clin. Oncol., 32 (12), 1256-1261
2. Friboulet et al. 2013. N. Engl. J. Med. 368 (12), 1101-1110.
3. Soria et al. 2017. J. Thorac. Oncol., 12 (1), S265-S266