The right drug, the right patient, the right time

Tumor-released circulating orphan non-coding RNAs reflect treatment response and survival in breast cancer

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Background

- Circulating tumor DNA (ctDNA) was recently shown to be a predictor of poor response and recurrence in breast cancer.
- ctDNA shedding from breast tumors rapidly decreases during treatment, resulting in reduced sensitivity in measuring tumor response.
- We recently reported the discovery of orphan non-coding RNAs (oncRNAs), as a large class of cancer specific small RNAs that are not present in healthy cells, but emerge from cancer cells.
- We hypothesized that oncRNAs provide an opportunity for a sensitive, rapid, and inexpensive liquid biopsy platform that does not require individualized assay development.

Annotating circulating orphan non-coding RNAs (oncRNAs):

- OncRNAs were annotated using small RNA sequencing across breast cancer cell lines from breast cancer patients (1) and lymphocytes from normal tissue.
- Analysis of extracellular compartment revealed that oncRNAs are secreted by cancer cells (2A) and we detected oncRNAs in sera from breast cancer patients (Fig 2B).
- We have since annotated more than 250,000 oncRNAs across human cancers using data from the Cancer Genome Atlas.

Patients and Methods

- Patients received standard NAC only (n=147) or with MK-2206 (n=64) or Pembo (n=53). Sera (1ml) were collected pretreatment (T0) and prior to surgery (T3) (Fig 2A).
- A universal “oncRNA fingerprinting” test was developed by extracting total cell-free RNA and cataloguing circulating oncRNAs detected using small RNA sequencing (Fig 3B).

Results

Rapid oncRNA fingerprinting in breast cancer patients:

- On average, we detected ~200 oncRNA species (per 10^6 reads mapped) in 1ml of serum from pre-treatment timepoints (T0; Fig 4).

Conclusions:

- OncRNAs provide a rapid (~4 days of processing), inexpensive, and robust approach to measure disease burden from ~1ml of serum.
- Our results highlight that oncRNA clearance in response to treatment is prognostic across multiple outcomes.
- Our preliminary results indicate that even after controlling for known markers such as pCR and RCB class, oncRNAs remained prognostic.
- We will next explore integration of other key clinical predictors (e.g. MRI and tumor volume) to further evaluate the clinical utility of oncRNAs in treatment planning.

Advocate perspective: Liquid biopsies have emerged as effective, non-invasive, diagnostic tools in disease monitoring and minimal residual disease detection. While ctDNA has been shown to be a significant predictor of poor response and metastatic recurrence, small non-coding RNAs (oncRNAs), actively released into the blood by some tumors, may provide a more sensitive biomarker. Identifying oncRNA in blood over time (before, during and after treatment) can enable providers to predict tumor response to therapy. This simple way to get at disease burden through serum, which does not require individualizing a test for each patient, could be rapidly generated, and may provide the complementary, more sensitive information to other circulating DNA tests.

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The drug is the right patient, the right time: novel liquid biomarkers for cancer detection and monitoring.