#4538: Genomic and proteomic predictors of sites of metastases in renal cell carcinoma

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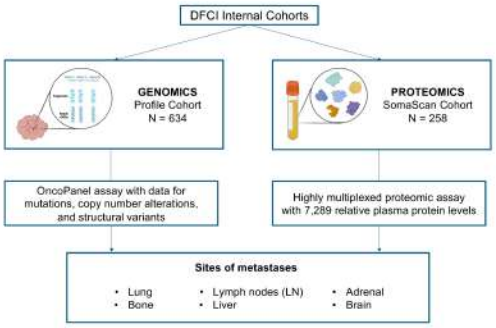
Background

- Among patients with renal cell carcinoma (RCC), the most common sites of metastasis are lung, lymph nodes, and bone. While some sites of metastases are associated with better cancer specific outcomes than others, the underlying biology of metastatic organ tropism is not well understood.
- Here, we performed genomic and proteomic analyses to investigate the biological underpinnings of different metastatic sites in RCC.

Methods

- Institutional cohorts of patients with metastatic RCC from the Dana-Farber Cancer Institute (DFCI) were analyzed using a next-generation tumor somatic mutation assay and a highly multiplexed plasma proteomics assay (**Fig. 1**). Clinical annotations for sites of RCC metastasis were curated.
- Genomic analyses were performed using a two-sided Fisher's exact test on the cBioPortal platform at DFCI with pairwise comparison of patients with versus without metastases to lung, liver, brain, bone, adrenal, and lymph nodes. The Benjamini-Hochberg method was applied for FDR-adjusted q-values.
- Exploratory proteomic analyses were performed using logistic regression for each metastatic site with multivariate adjustment for other sites of metastasis. For each metastatic site, the top five associated proteins were selected to build a multivariate model to predict the presence of each metastatic site. Bootstrapping with R = 1,000 was employed for the assessment of model performance.

Fig. 1: Study Flow Chart



Results

Fig. 2: Tumor genomic alterations associated with lung metastases

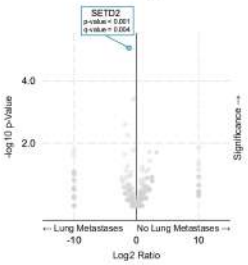
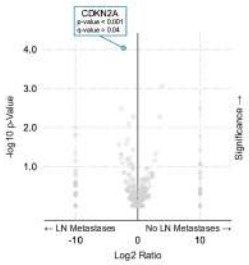
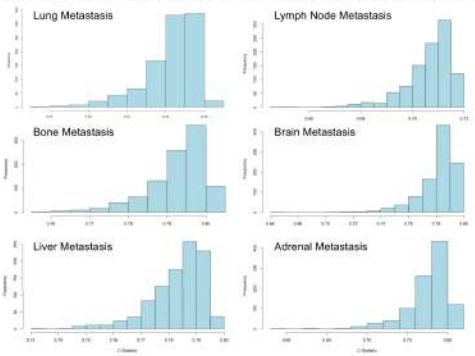


Fig. 3: Tumor genomic alterations associated with nodal metastases



- Tumor genomic alterations in *SETD2* (q-value=0.004) and *CDKN2A* (q-value=0.04) were associated with lung and lymph node metastases, respectively (**Fig. 2 + 3**).
- Circulating collagen alpha-1(IX) chain (CO9A1) and relaxin receptor 1 (RXFP1) were the top circulating proteins associated with bone metastases (both p-value<0.001), while tenascin (p-value<0.001) and GGT2 (p-value=0.001) were associated with liver metastases, and matrilysin (MMP-7) was associated with lymph node metastases (p-value=0.003).

Fig. 4: Bootstrap distribution of C-statistics for predicting metastasis



- Multivariate models using the top five proteins to predict the presence of each metastatic site demonstrated bootstrapped C-statistics from 0.72 to 0.80 for lymph nodes, lung, adrenal, brain, liver, and bone metastasis (**Fig. 4**).

In genomic and proteomic analyses, both tissue-based and circulating predictors were identified for different metastatic sites in RCC. Proteomic model performance to predict metastatic sites showed C-indices from 0.72 to 0.8.

Future work will focus on validating these findings in independent external cohorts and adding transcriptomic analyses for an integrative characterization of metastatic organ tropism in RCC.

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