(MP08-12) Transcriptional programs in clear cell renal cell carcinomas with necrosis on imaging

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Introduction

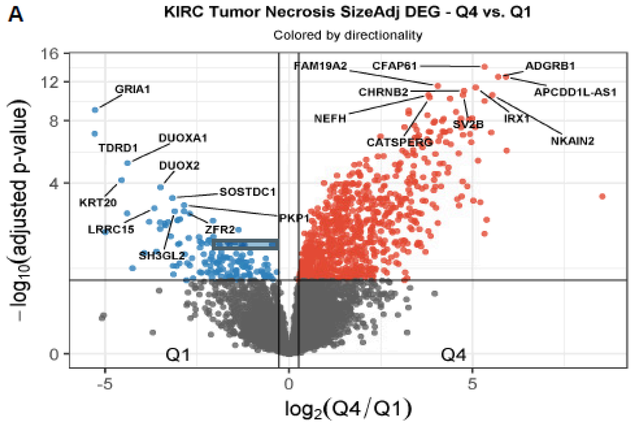
Tumor necrosis has been widely acknowledged as an adverse factor in patients with renal cell carcinoma (RCC). Furthermore, it has been shown that the proportion of non-enhancing tumor (NT) volume on computed tomography (CT) can predict the presence of necrosis at the histologic level, with a relatively high degree of accuracy. However, it is not clear which cellular processes lead to necrosis or non-enhancement (on CT) in primary renal tumors. Therefore we analyzed imaging and transcriptomic data from the TCGA clear cell RCC (ccRCC) cohort to look for differences in gene expression of tumors with and without necrosis.

Methods

- Imaging data from 183 patients from the TCGA ccRCC cohort (Firas et al.) was retrieved. The clinicopathological and RNAseq data was obtained from the GDC portal.
- Differential gene expression (DGE) analysis was performed to compare necrotic (non-enhancing) versus non-necrotic (enhancing) tumors.
- Ingenuity pathway analysis was performed using the top differentially-expressed genes to explore the most relevant cellular pathways involved.
- The Benjamini-Hochberg approach was used to correct for multiple testing and a q-value (FDR-corrected) of less than 0.05 was used to define statistical significance.

Results

- Of the 183 patients included, 110 (61%) were stage I/II, 48 (26%) were stage III, and 25 (14%) were stage IV.
- The median tumor size was 5 cm (range 1-17) and the median proportion of non-enhancing tumor was 8% (IQR 3-17%).
- The top five differentially-expressed genes were *CFAP61*, *APCDD1L-AS1*, *ADGRB1*, *FAM19A2*, *IRX1* (all q<0.001), and they all showed higher expression in non-enhancing tumors (Figure 1A).
- The top differentially-expressed pathways were *'BRCA1* DNA Damage Response', 'Cell Cycle Control of Chromosomal Replication', and 'CHK Proteins in Cell Cycle Checkpoint Regulation' (all q<0.001), suggesting that necrotic ccRCC tumors have higher proliferation and interferon mediated immune infiltration than non-necrotic tumors (Figure 1B).



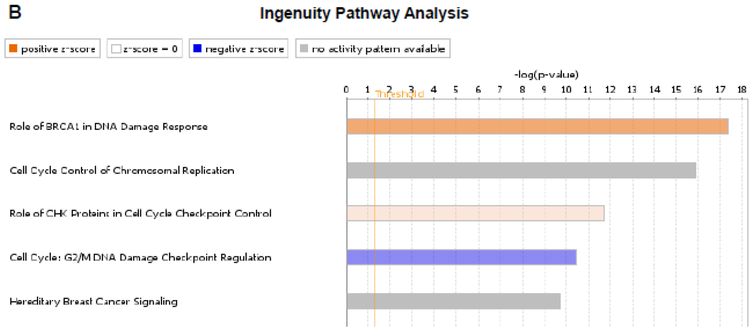


Figure 1: A. Differential gene expression comparing necrotic (non-enhancing) versus non-necrotic (enhancing) tumors **B.** Ingenuity pathway analysis using top differentially-expressed genes

Conclusions

- There are significant differences in the gene expression profile of enhancing and non-enhancing tumors.
- DNA damage, immune response, and cell cycle regulation pathways seem to have differential activity between enhancing and non-enhancing tumors.
- Ongoing work is underway to determine whether imaging necrosis can serve as a biomarker for immunotherapy response in ccRCC.