Transcriptomics landscape of Necroptosis genes is associated with Dendritic cells infiltration: a pan-cancer study of 5,451 primary solid tumors.

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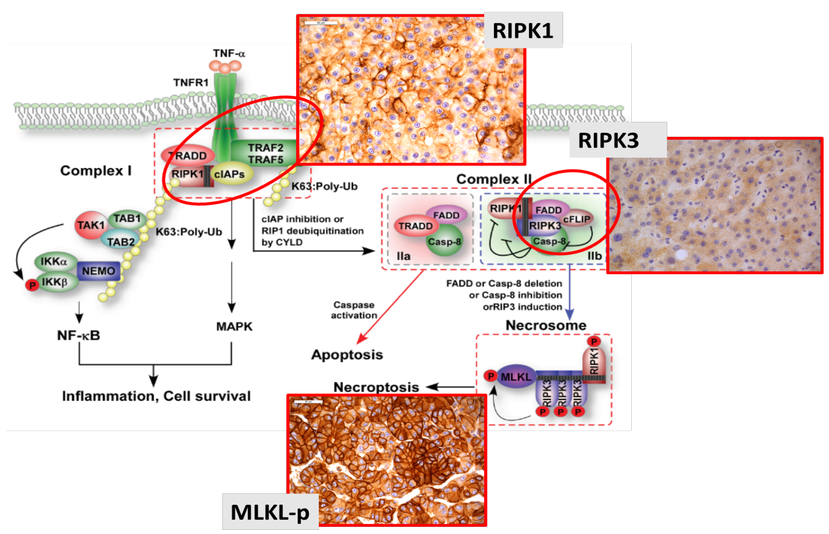
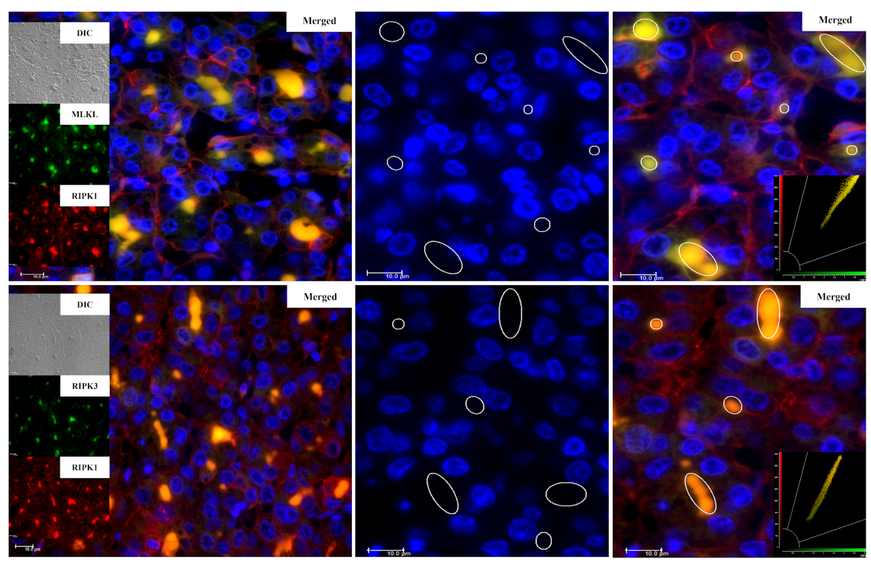
BACKGROUND

- **Necroptosis** (NPC) is a form of programmed cell death that culminates with the rupture of the cell membrane followed by the releasing of cellular elements[1].
- Evidence showed that tumors with high expression of NCP-related genes are associated with high cytotoxic CD8+ T-cell infiltrates, mediated by signaling from Dendritic (DC) and CD4+ T-cells[2].





AIM

- Pan-cancer view of the relationship between NCP and immune infiltration and their prognostic relevance across 24 cancer types from The Cancer Genome Atlas.
- Evaluate whether there are some immune populations able to interact more with NCP in specific cancer types.

METHODS

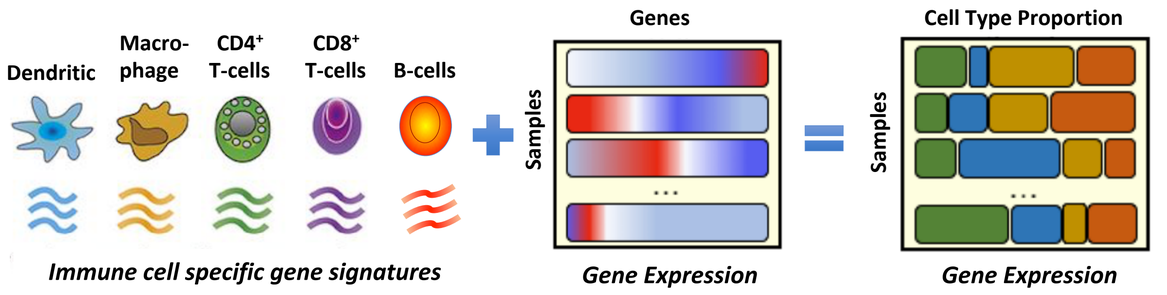
5,451 Primary Solid Tumors

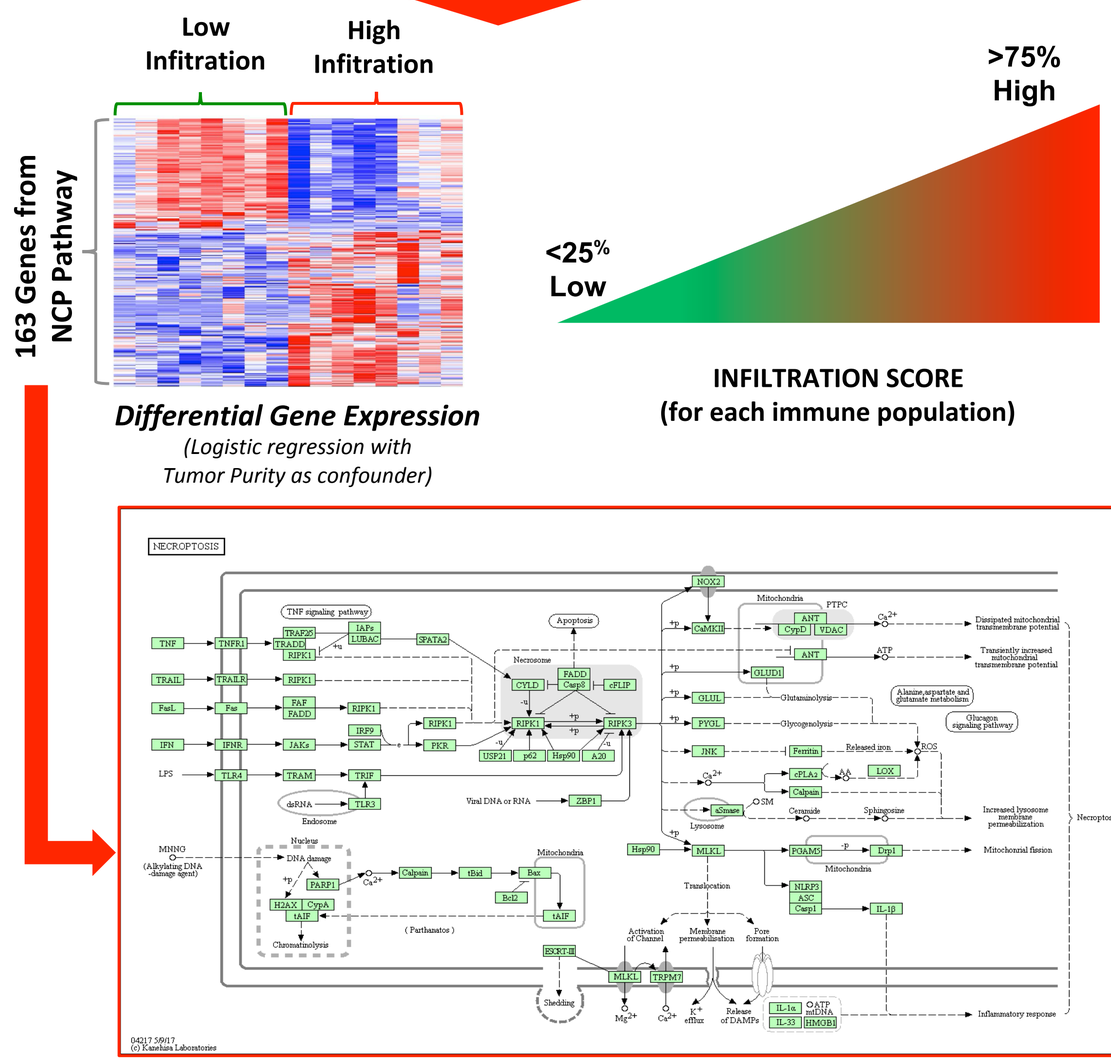
Filter **RNAseq data**

- **No residual tumor after surgery**
- **No previous treatment**

Mixture tissue Transcriptome

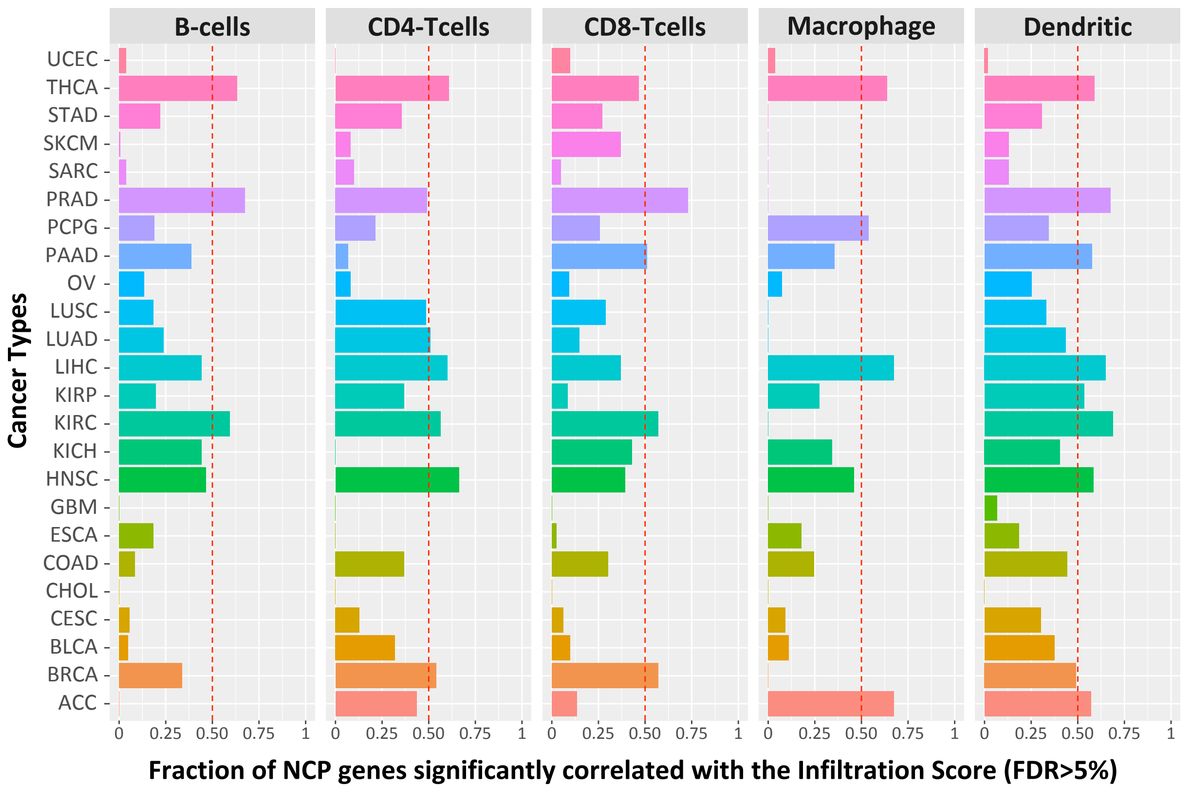
Cell-type Deconvolution (TIMER)[3]



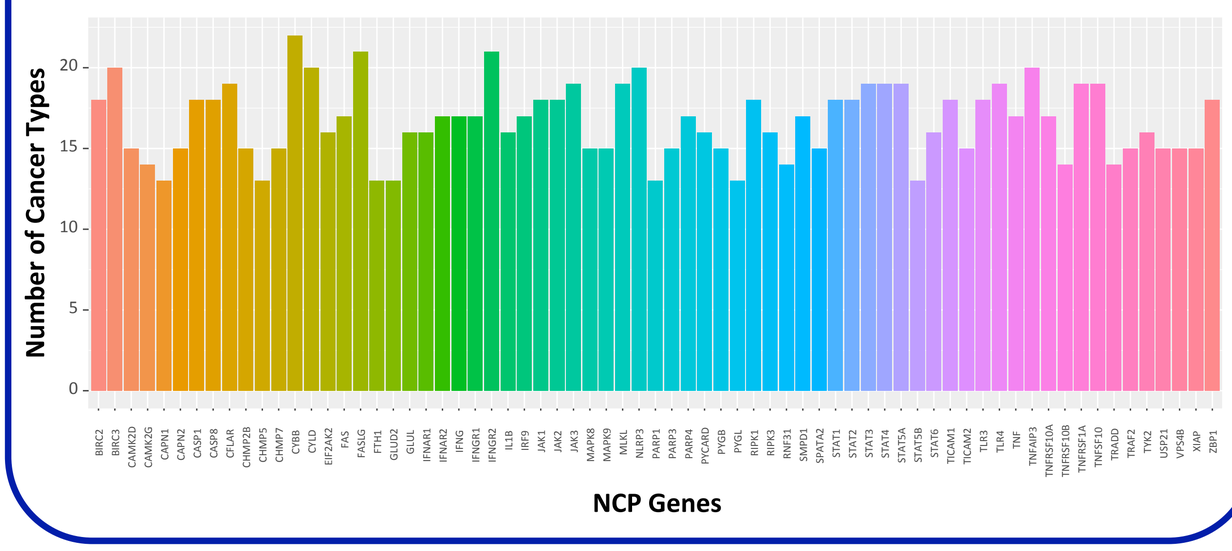


RESULTS

- Dendritic and CD4+ T-cells showed the highest number of cancer types (8) reporting more than half genes of NCP pathway significantly correlated with their infiltration. CD8+ T-cell infiltration correlated with >50% of NCP genes in 5 of these 8 cancer types: Kidney-Renal, Breast, Prostate, Pancreatic and Thyroid tumors.



- Dendritic cells also showed the highest number of NCP genes (69) correlated with their infiltration in more than half of the analyzed cancer types, including the main genes involved in NCP execution: RIPK1, RIPK3, MLKL and CFLAR. 60 and 58 of these genes showed a prognostic relevance (p<5%) for overall and disease-free survival in at least one cancer type, respectively.



CONCLUSIONS

NCP has a relevant role in eliciting immune response against tumor through Dendritic cell-mediated immunity in specific cancer types, however validation studies on specific cancer type are needed.

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REFERENCES

1. Meng M, Wang H, Cui Y, et al. Necroptosis in tumorigenesis, activation of anti-tumor immunity, and cancer therapy. Oncotarget. 2016;7(35):57391.
2. Aaes T, Kaczmarek A, Delvaeye T, et al. Vaccination with necroptotic cancer cells induces efficient anti-tumor immunity. Cell Reports. 2016;15(2):274-287.
3. Li T, Fan J, Wang B, Traugh N, Chen Q, Liu JS, Li B, Liu XS. TIMER: A Web Server for Comprehensive Analysis of Tumor-Infiltrating Immune Cells. Cancer Res. 2017;77(21):e108-e110

METHODS: Computational Analysis – *Transcriptomics data*

TCGA

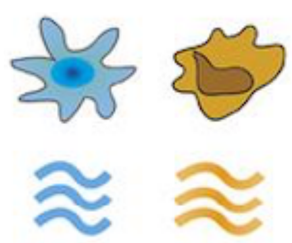
5,451 Primary Solid Tumors

Filter **Whole RNAseq data**

- **No residual tumor after surgery**
- **No previous treatment**

Mixture tissue Transcriptome

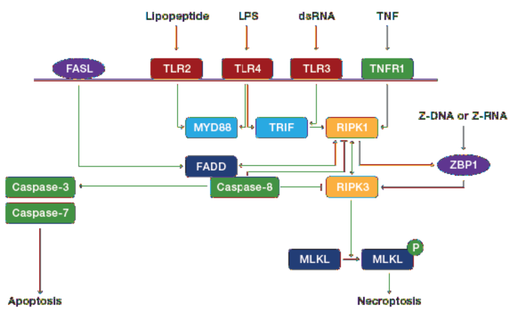
TIMER Deconvolution



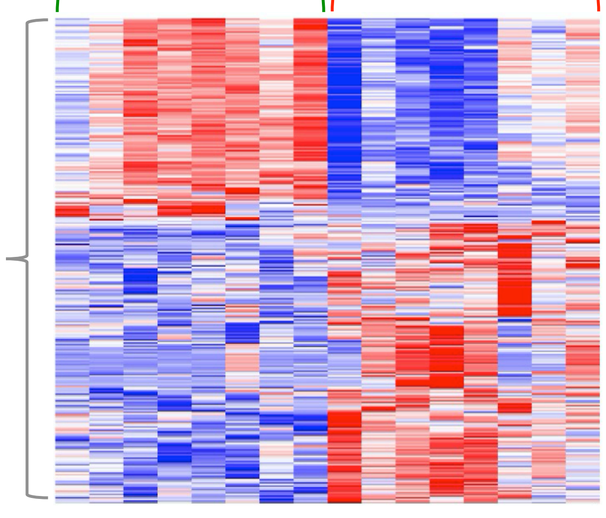
B-cells
CD4 T-cells
CD8 T-cells
Macrophages
Dendritic cells

Immune Cell infiltration score

Genes from KEGG Necroptosis (163)



Low Infitration **High Infitration**



Differential Gene Expression

(Logistic regression with Tumor Purity as confounder)

>75th percentiles High infiltration

<25th percentiles Low infiltration

METHODS: Gene expression RNA-seq data from 5,451 primary solid tumors were considered, excluding cases with treatments before surgery and with residual tumor. A deconvolution algorithm was used to estimate the level of tumor-infiltrating immune cells in each RNA-seq sample, considering the populations: B-cells, CD4 T-cells, CD8 T-cells, Macrophages and DC. For each immune population, the relative infiltration score was dichotomized at low and high infiltration using the 25th and 75h percentiles, respectively. Logistic regression and likelihood ratio test were applied to 163 genes belonging to Necroptosis pathway from KEGG database to test whether they are significantly associated to the infiltration of a specific immune population. FDR-adjusted p-values <5% were considered statistically significant. The prognostic relevance of the NCP genes significantly correlated with the infiltration was evaluated by Cox regression and log-rank test.

Li et al. *Genome Biology* 2016;17(1):174.