The correlation between non-coding RNA and response rate to immune-checkpoint inhibitors.

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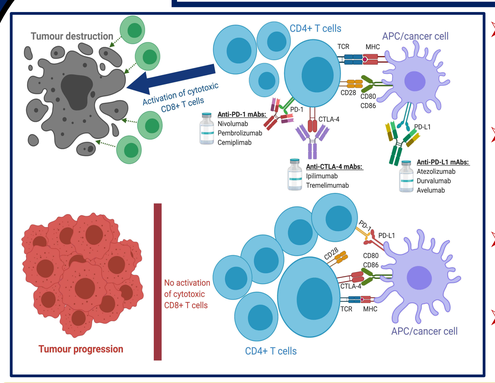
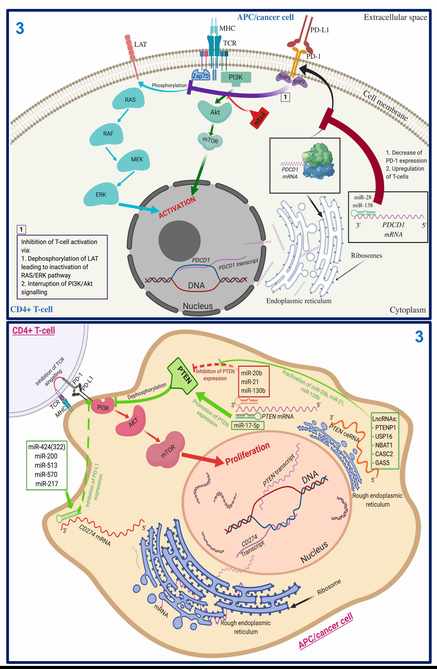
INTRODUCTION



- ICIs are **monoclonal antibodies** that neutralise inhibitory CTLA-4 and PD-1 signalling pathways and thus **boosting cytotoxic T cell** antitumor activity
- ICIs have already **transformed** clinical guidelines for NSCLC, renal cell carcinoma, metastatic melanoma, hepatocellular carcinoma
- At least 50% of treated patients develop immune-related adverse events with **NO** risk factors/mechanisms known to date [1]
- PD-L1 expression, BMI, dNLR are associated with ICI efficacy, albeit with **NO** established mechanisms [2]

Identification of: (1) **risk factors of ICI therapy**; (2) **responsible mechanisms** and (3) **therapeutic agents** interfering within involved pathways may markedly improve ICI treatment outcomes and thus herald a new era of **personalized and safe ICI anticancer treatment**.

- **70%** of human genome is converted into non-coding RNA
- **1965** – discovery of first ncRNA (transfer RNA)
- **1998** – C. Melo and A. Fire revealed the mechanism of how ncRNA control gene expression
- Both microRNA and lncRNA can promote **cancer drug resistance** to chemo- and radiation therapy



- **miRNAs** create RISC complex with Ago1 and Ago2 proteins which then bind to 3' UTR of mRNA and repress translation or boost cleaving of mRNA
- **lncRNAs** control RNA polymerase expression, mRNA splicing and act as ceRNA (pseudogenes)
- miR-28, miR-138, miR-424 can **inhibit** expression of immune checkpoints in both cancer and T cells
- lncRNAs PTENP1, USP16, NBAT1 can **interfere** within **PI3K/Akt** pathway responsible for PD-1 signaling

Does ncRNA affect the response rate to immune-checkpoint inhibitors ?

METHODS

NCBI GEO database (Gene Expression Omnibus)

- Meta-analysis was conducted in **STATA** v16
- **Standardized mean difference** (SMD) used as effect-size
- SMD was calculated with ***Hedges' g*** method
- **I^2** and **T^2** used to test study heterogeneity
- **DAVID** online bioinformatic was used to elaborate mechanisms

Datasets were considered eligible if:

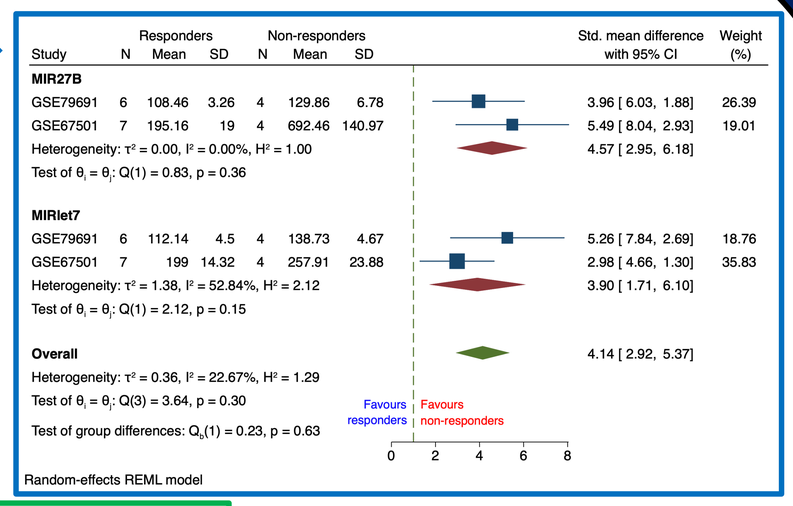
- Study treatment was ICIs
- Study analyzed RNA within two groups of patients: **(1)** with complete or partial response; **(2)** stable disease or disease progression
- Study analyzed coding and non-coding RNAs

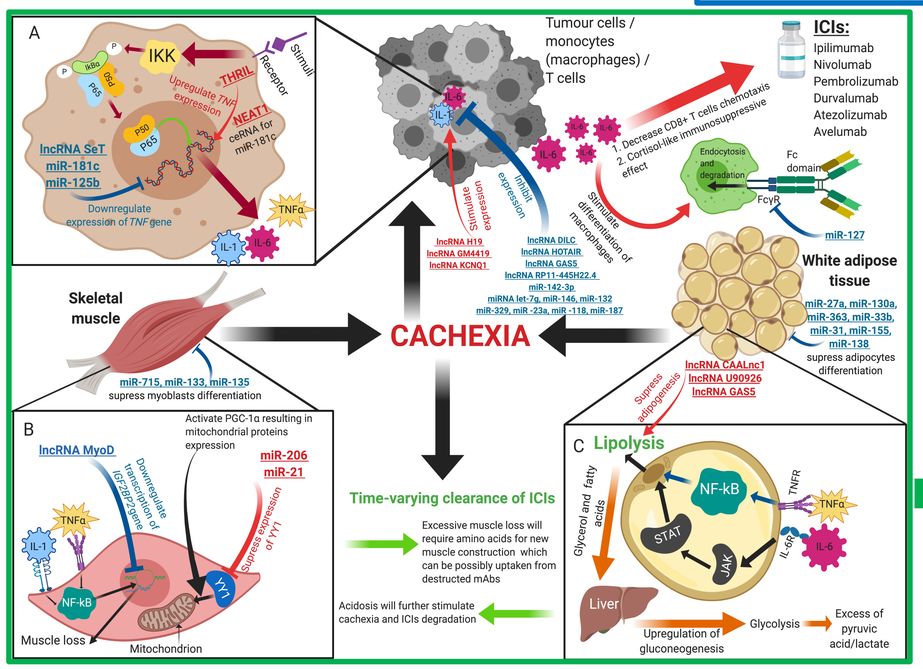
For comparison we selected studies of the similar design, except study treatment was **not** ICIs

RESULTS

Datasets of interest:

- **GSE79691** (metastatic melanoma) and **GSE67501** (renal cell carcinoma)
- Treatment with **Nivolumab**
- RNA was obtained from FFPE samples
- **MiR-27B** (p=0.02) and **miR-let7D** (p=0.003) were significantly higher among non-responders
- SMD was 4.57 (miR-27B) and 3.9 (miR-let7D) higher among non-responders
- **Low** study **heterogeneity** scores: I^2=22.67% and T^2=0.36

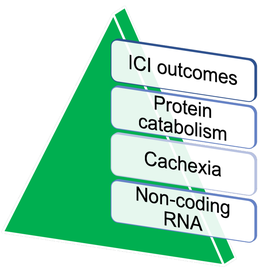




Control datasets:

- **GSE99898** (metastatic melanoma) and **GSE74174** (renal cell carcinoma)
- Treatment with **kinase inhibitors**
- RNA was obtained from FFPE samples
- Expression of miR-27B (p=0.928) and miR-let7D (p=0.41) was **not significantly** different among responders and non-responders

"Obesity paradox" is commonly observed among ICI-treated patients (patients with BMI>25 have better response comparing to patients with BMI<25) [4]



Mechanisms (DAVID online tool):

- Both miRNA may regulate **pro-cachexia cytokines** (IL-1, IL-6, TNF-α) and **PI3K/Akt** and **NF-kB** signalling pathways
- Said cytokines may stimulate **FcR-mediated clearance** of immunoglobulins
- Cachexia itself may promote the **destruction of circulating proteins**, particularly ICIs

CONCLUSIONS

- **MiR-27B** and **miR-let7D** are significantly higher among **non-responders** to ICI therapy, supporting their possible predictive role
- There is **NO difference** in expression of said miRNAs among responders and non-responders treated with non-ICI therapeutic regimens
- Both miRNAs can **interfere** with **different** signalling pathways (PI3K/Akt, NF-kB) and **regulate cachexia**

PERSPECTIVES

Risk factors of Immune-ChEckpoint inhibitors MEdiated Liver, endocrine, skin and gastrointestinal Toxicity

ICEMELT study

Design:
Multicenter prospective cohort study
Location:
Sydney, New South Wales, Australia
Results:
Preliminary results are anticipated by March 2022

2020 – 2024

Research aims:

- To identify ncRNAs significantly associated with irAEs
- To reveal responsible pathways/mechanisms of such association
- To establish therapeutic targets interfering with found mechanisms, thus enhancing clinical outcomes of cancer immunotherapy

Abbreviations: ICIs – immune-checkpoint inhibitors; FDA – Food and Drug Administration; ncRNA – non-coding RNA; miR – microRNA; lncRNA – long non-coding RNA; SMD – standardized mean difference; BMI – body mass index; dNLR – derived neutrophil-to-lymphocyte ratio; NSCLC– non-small cell lung cancer; irAEs – immune-related adverse events; FFPE – formalin-fixed paraffin embedded.

NO CONFLICTS OF INTEREST TO DECLARE

References: 1 – Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol.* 2018;36(17):1714-1768. 2 – Nakamura Y. Biomarkers for Immune Checkpoint Inhibitor-Mediated Tumor Response and Adverse Events. *Front Med (Lausanne).* 2019;6:119. 3 – Shek D, Read SA, Akhuba L, et al. Non-coding RNA and immune-checkpoint inhibitors: friends or foes? *Immunotherapy.* 2020;12(7):513-529. 4 – Donnelly D, Bajaj S, Yu J, et al. The complex relationship between body mass index and response to immune checkpoint inhibition in metastatic melanoma patients. *J Immunother Cancer.* 2019;7(1):222.