



Glycolytic metabolism plays a leading role in cancer. How to fight this reprogramming?

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Background: Metabolic reprogramming is a process by which cancer cells adapt to meet the increasing energy demand. The aim of this study is to identify new therapeutic targets exploiting metabolic reprogramming to selectively hit cancer cells. In particular, the work focuses on the RNA-binding role of phosphoglycerate kinase 1 (PGK1), a glycolytic enzyme involved in ATP production.

Methods: A selection of genes involved in metabolism from KEGG and Reactome Pathways databases ($n = 1095$) was used to filter gene expression data of the GTEx and PCAWG projects, relating to healthy and cancer tissues, respectively. The expression data was obtained from the ICGC data portal and analysed with the R programming language to identify genes deregulated in cancer ($n = 289$).

The HybridRNAbind meta-predictor was used to identify amino acid residues involved in RNA binding in selected proteins, and mutants showing missense mutations possibly affecting RNA binding sites were identified via the COSMIC database.

Wild-type protein and selected mutants were expressed in *E. Coli* strain BL21(DE3) and purified to study the effect of mutations on RNA binding.

Results: Among up-regulated genes in tumours, we focused our interest on PGK1 since its overexpression (also at the protein level in various tumours, such as ovarian, uterine and lung, as identified via the UALCAN portal), and its known RNA-binding capability. PGK1 missense mutations and their RNA-binding residues were structurally analysed, and the following selected mutants were expressed and purified, along with the wild-type counterpart, for further experimental analyses: R38M, H62Y, R65W, G166D, F241S, S45N.

Conclusion: Considering the overexpression of PGK1, both at gene and protein levels, and its known role as RNA-binding protein, we would like to investigate if mutations affect RNA-binding affinity and the biological consequences of this binding in tumours, using a computational and experimental approach.