TITOLO DEL POSTER

Autori e affiliazioni

ROLE OF DIACYLGLYCEROL KINASES IN ACUTE MYELOID LEUKEMIA

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Acute myeloid leukemia (AML) is an aggressive hematological disorder mainly affecting people of older age. While studying the reasons behind the exponential increase of AML incidence with age, a potential role of diacylglycerol kinases in AML development was observed.

Diacylglycerol kinases (DGK) are a family of regulators of lipid signaling that decrease diacylglycerol signaling while producing phosphatidic acid, a bioactive lipid by itself. DGK activity is known to play a role in cell transformation but also in immunosurveillance against tumors. DGK's role in tumor cells prompted the biochemistry research group of the Center for translational research on allergic and autoimmune diseases of Eastern Piedmont University to develop novel DGK inhibitors with potential applications to genetic and oncological diseases.

The potential role of DGKs in AML emerged from an exploration of the TGCA and GTEx databases with the GEPIA2 tool that highlights DGK's overexpression in AML tumor tissue when compared to control tissues. Among the 10 DGK isoforms known, specifically DGKA, DGKD, DGKE, DGKG and DGKZ are significatively overexpressed in AML tumor tissue. An increased expression of DGKA, DGKD, DGKG and DGKQ was also notable in expression data from BeatAML2 database when comparing AML tumor cells with CD34+ controls. When observing overall survival, DGKA and DGKE are negative prognostic markers, while high DGKG expression leads to a more favorable prognosis and DGKD or DGKZ do not correlate with survival. Those data suggest and alteration of diacylglycerol signaling in AML and a specific contribution of each DGK isoform to cell transformation.

To experimentally validate those results we explored the sensitivity of the HL-60 cellular model to the available DGK inhibitors and compared it to other lymphoma models (Jurkat cells) or primary peripheral blood derived mononucleated cells (PBMC). We observed a selective sensitivity of HL-60 to DGK inhibitors in line with a specific function of those enzyme in AML biology.

Those preliminary data suggest the opportunity to further explore the biological role of DGK in AML and their potential utility as therapeutic targets.

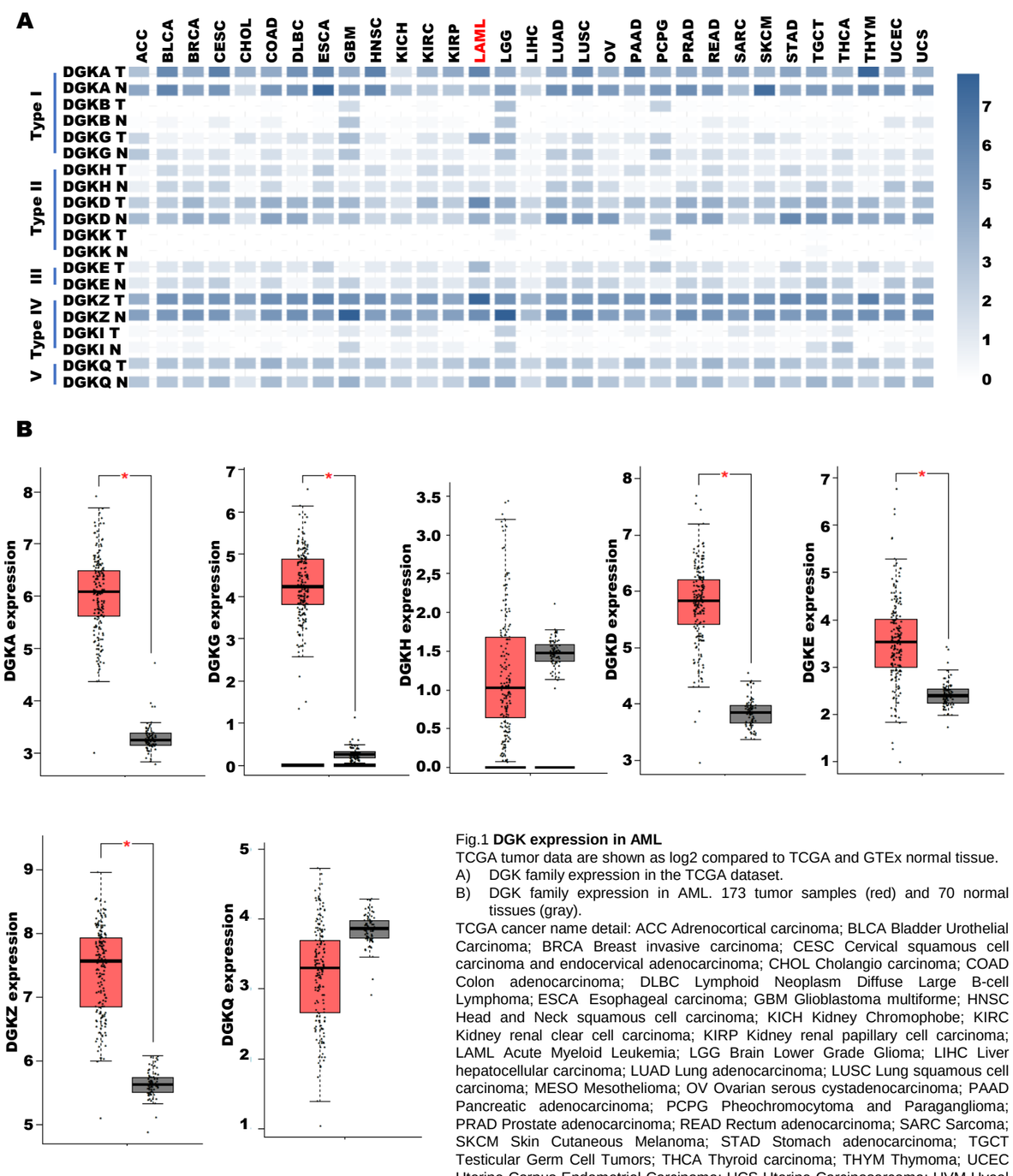

Fig.1 **DGK expression in AML**
TCGA tumor data are shown as log2 compared to TCGA and GTEx normal tissue.
A) DGK family expression in the TCGA dataset.
B) DGK family expression in AML. 173 tumor samples (red) and 70 normal tissues (gray).

TCGA cancer name detail: ACC Adrenocortical carcinoma; BLCA Bladder Urothelial Carcinoma; BRCA Breast invasive carcinoma; CESC Cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL Cholangio carcinoma; COAD Colon adenocarcinoma; DLBC Lymphoid Neoplasm Diffuse Large B-cell Lymphoma; ESCA Esophageal carcinoma; GBM Glioblastoma multiforme; HNSC Head and Neck squamous cell carcinoma; KICH Kidney Chromophobe; KIRC Kidney renal clear cell carcinoma; KIRP Kidney renal papillary cell carcinoma; LAML Acute Myeloid Leukemia; LGG Brain Lower Grade Glioma; LIHC Liver hepatocellular carcinoma; LUAD Lung adenocarcinoma; LUSC Lung squamous cell carcinoma; MESO Mesothelioma; OV Ovarian serous cystadenocarcinoma; PAAD Pancreatic adenocarcinoma; PCPG Pheochromocytoma and Paraganglioma; PRAD Prostate adenocarcinoma; READ Rectum adenocarcinoma; SARC Sarcoma; SKCM Skin Cutaneous Melanoma; STAD Stomach adenocarcinoma; TGCT Testicular Germ Cell Tumors; THCA Thyroid carcinoma; THYM Thymoma; UCEC Uterine Corpus Endometrial Carcinoma; UCS Uterine Carcinosarcoma; UVM Uveal Melanoma.

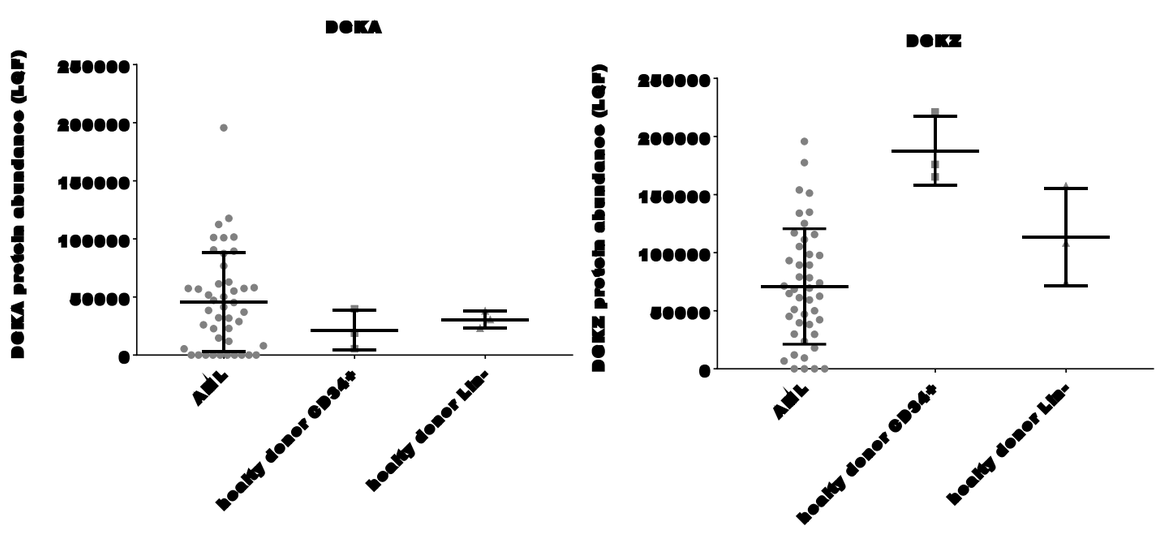

Fig.2 **DGKA and DGKZ protein expression in AML**
Label-free-quantification (LFQ) protein abundance measurements from 44 adult patients from the TCGA dataset with de novo AML as well as a number of healthy donors (HD).

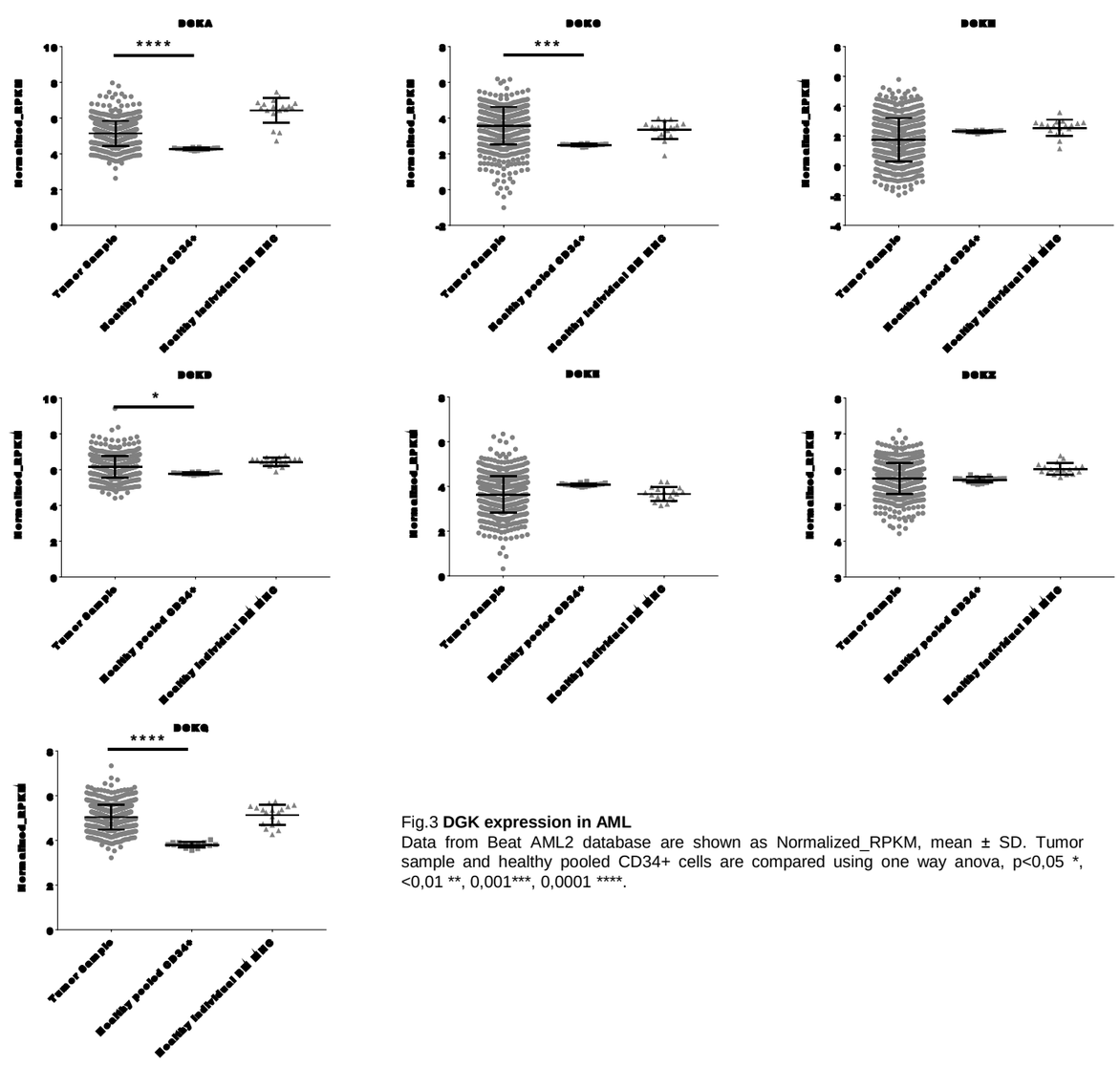

Fig.3 **DGK expression in AML**
Data from Beat AML2 database are shown as Normalized_RPKM, mean ± SD. Tumor sample and healthy pooled CD34+ cells are compared using one way anova, p<0,05 *, <0,01 **, 0,001***, 0,0001 ****.

Fig.2 **DGK expression and survival in AML**
High DGK group is shown in **red**, low DGK in **blue** together with 95% confidence interval (dotted lines), n(high)=27, n(low)=27.

- DGKA Logrank p=0.05, hazard ratio (high) 2.3 with p=0.05;
- DGKG Logrank p=0.05, hazard ratio (high) 0.4 with p=0.05;
- DGKH Logrank p=0.85; hazard ratio (high) 1.1 with p=0.85
- DGKD Logrank p=0.69, hazard ratio (high) 0.86 with p=0.69;
- DGKE Logrank p=0.06, hazard ratio (high) 2.2 with p=0.07;
- DGKZ Logrank p=0.48, hazard ratio (high) 0,7 with p=0.49;
- DGKQ Logrank p=0.34, hazard ratio (high) 1.4 with p=0.34;