TRANSCRIPTOME PROFILING OF ST3GAL4 AND FUT7 IN MULTIPLE TUMOR TYPES AND PROGNOSTIC VALUE IN ADULT ACUTE MYELOID LEUKEMIA

William E. Fogler1, Vince Deng2, David Stewart1, Michael Jamari3, Simone Damineli4, Adrián Carr1, John L. Magnani1

GlycoMimetics, Inc., Rockville, MD, Fos Genomics, Ltd., Edinburgh, UK

Abstract

E-selectin is a cell adhesion glycoprotein expressed on endothelial cells and participates in the development of environmental and drug-mediated resistance and poor clinical outcome in cancer. The E-selectin antagonist, uproleselan, is currently in clinical trials in patients with urothelial bladder carcinoma, given to upregulate, linking E-selectin ligand expression to response. Multiple genes involved in the glycan synthesis of E-selectin ligands are highly expressed in pediatric AML. Clinical and RNA-seq expression data for 10,258 samples covering 33 cancer types from the PanCanAtlas of The Cancer Genome Atlas (TCGA) were accessed via the NCBI Gene Expression Omnibus (GEO). The number of samples from each tumor type varied, ranging from 45 samples which were available for cholangiocarcinoma (CHOL) to 1,388 for breast invasive carcinoma (BRCA), with a median of 198 samples/tumor type. Expression data was log2 transformed. Where no sequencing reads from a gene were detected in a sample, a low (non-) zero value was assigned to that sample by the PanCanAtlas. The expression levels of two of these genes, ST3GAL4 and FUT7 are associated with poor outcome and are associated with cell surface E-selectin ligand expression. In the current study we extend transcriptome profiling of E-selectin ligand forming glycosylation genes with an emphasis on ST3GAL4 and FUT7 in different cancer cell lines and primary patient samples.

Results

1. Expression Levels of FUT7 (A) and ST3GAL4 (B) in Each of the 33 Cancer Types in the PanCanAtlas

Clinical and RNA-seq expression data for 10,258 samples covering 33 cancer types from the PanCanAtlas of The Cancer Genome Atlas (TCGA) were accessed via the NCBI Gene Expression Omnibus (GEO). The number of samples from each tumor type varied, ranging from 45 samples which were available for cholangiocarcinoma (CHOL) to 1,388 for breast invasive carcinoma (BRCA), with a median of 198 samples/tumor type. Expression data was log2 transformed. Where no sequencing reads from a gene were detected in a sample, a low (non-) zero value was assigned to that sample by the PanCanAtlas. The expression levels of two of these genes, ST3GAL4 and FUT7 are associated with poor outcome and are associated with cell surface E-selectin ligand expression. In the current study we extend transcriptome profiling of E-selectin ligand forming glycosylation genes with an emphasis on ST3GAL4 and FUT7 in different cancer cell lines and primary patient samples.

2. Expression Levels of FUT7 (A) and ST3GAL4 (B) in the 1457 Cell Lines in the Cancer Cell Line Encyclopedia (CCLE)

The E-selectin ligand glycosylation genes, FUT7 and ST3GAL4, are also consistently expressed in tumor cell lines comprising the Cancer Cell Line Encyclopedia (CCLE) data base. The top five cancer types, based on mean expression:

- FUT7: T Cell Lymphoma, AML, B cell Acute Lymphoblastic Leukemia, Other Leukemias and Chronic Myelogenous Leukemia (CML)

3. Expression Levels of FUT7 (A) and ST3GAL4 (B) in the TCGA-LAML FL3 Data Set

The TCGA-LAML RNAseq dataset was characterized for expression of FUT7 and ST3GAL4. The dataset included 142 RNAseq profiles of bone marrow samples from patients with AML, with corresponding survival time data, and within this dataset the status of the FMS-like tyrosine kinase 3 (FLT3) proto-oncogene was considered. Mutational alterations of FLT3 are associated with higher risk of relapse and shorter OS compared with wild-type FLT3. ST3GAL4 and FUT7 were both identified as being upregulated (fold-change = 1.73 and 1.40, respectively) in the mutated FLT3 subset (n=44) as compared to wild type FLT3 (p=0.000533 and 0.046, respectively). Notably in the FL3-T3 ITD mutated subset, expression of FUT7 was significantly associated with a poor prognosis and decreased OS (HR = 0.223, p<0.015). Collectively, these studies extend the prognostic importance of the E-selectin ligand glycosylation genes, ST3GAL4 and FUT7, to adult AML where these genes may be useful as predictive biomarkers. In addition, these studies suggest potential additional tumor types beyond AML where treatment protocols with uproleselan may have therapeutic benefits.

Conclusions

- These studies extend the prognostic importance of the E-selectin ligand glycosylation genes FUT7 and ST3GAL4 to adult AML.
- AML patients harboring the FLT3 ITD mutation with high expression of FUT7 or ST3GAL4 experience poor survival, in contrast to patients with low expression of FUT7 or ST3GAL4.
- These studies suggest additional tumor types beyond AML where treatment protocols with the E-selectin antagonist, uproleselan may have therapeutic benefits.

References


Results (cont.)

Results (cont.)

Figure 1. Expression Levels of FUT7 (A) and ST3GAL4 (B) in Each of the 33 Cancer Types in the PanCanAtlas

Clinical and RNA-seq expression data for 10,258 samples covering 33 cancer types from the PanCanAtlas of The Cancer Genome Atlas (TCGA) were accessed via the NCBI Gene Expression Omnibus (GEO). The number of samples from each tumor type varied, ranging from 45 samples which were available for cholangiocarcinoma (CHOL) to 1,388 for breast invasive carcinoma (BRCA), with a median of 198 samples/tumor type. Expression data was log2 transformed. Where no sequencing reads from a gene were detected in a sample, a low (non-) zero value was assigned to that sample by the PanCanAtlas. The expression levels of two of these genes, ST3GAL4 and FUT7 are associated with poor outcome and are associated with cell surface E-selectin ligand expression. In the current study we extend transcriptome profiling of E-selectin ligand forming glycosylation genes with an emphasis on ST3GAL4 and FUT7 in different cancer cell lines and primary patient samples.

Figure 2. Expression Levels of FUT7 (A) and ST3GAL4 (B) in the 1457 Cell Lines in the Cancer Cell Line Encyclopedia (CCEL)

The E-selectin ligand glycosylation genes, FUT7 and ST3GAL4, are also consistently expressed in tumor cell lines comprising the Cancer Cell Line Encyclopedia (CCLE) data base. The top five cancer types, based on mean expression:

- FUT7: T Cell Lymphoma, AML, B cell Acute Lymphoblastic Leukemia, Other Leukemias and Chronic Myelogenous Leukemia (CML)

Figure 3. Expression Levels of FUT7 (A) or ST3GAL4 (B) in the FL3-T3 ITD AML Patient Defines Poor Outcome

Survival analysis was performed with the Cox proportional model, associating the expression of E-selectin ligand glycosylation genes, FUT7 or ST3GAL4, with overall survival (OS). Expression levels for each gene were dichotomized (high or low) using the median expression value over the full set of samples.

Conclusions

- These studies extend the prognostic importance of the E-selectin ligand glycosylation genes FUT7 and ST3GAL4 to adult AML.
- AML patients harboring the FLT3 ITD mutation with high expression of FUT7 or ST3GAL4 experience poor survival, in contrast to patients with low expression of FUT7 or ST3GAL4.
- These studies suggest additional tumor types beyond AML where treatment protocols with the E-selectin antagonist, uproleselan may have therapeutic benefits.

Background

- Recent clinical data has demonstrated a correlation between AML cell surface E-selectin ligand expression and response to uproleselan (DeAngelo et al., 2018).
- In pediatric AML the high expression of two genes involved in the glycan synthesis of E-selectin ligands, FUT7 and ST3GAL4, are associated with poor outcome and cell surface E-selectin ligand expression (Leoni et al., 2019).
- In the current transcriptome profiling of the E-selectin ligand forming glycosylation genes, FUT7 and ST3GAL4 and has been extended to different tumors and included adult AML.

Figure 3. Expression Levels of FUT7 (A) or ST3GAL4 (B) in the FL3-T3 ITD AML Patient Defines Poor Outcome