Overview

Acute Myeloid Leukaemia (AML) is a blood cancer thought to be the result of a combination of genetic alterations and aberrant gene expression patterns.

It is characterised by the overproduction of immature white blood cells in the bone marrow. The proliferating cells cause disease by swamping the production of normal blood cells.

AML makes up about 1 percent of cancers, and is the second most common type of leukaemia diagnosed in adults and children.

Relapse and chemotherapy resistance are the main challenges of AML care.

40 to 60 percent of adults and 30 to 40 percent of children relapse within three years.

5-year overall survival rates are 28 percent for adults and 70 percent for children.

Dr Linda Holmfeldt, Principal Investigator in the department of Immunology, Genetics and Pathology at Uppsala University in Sweden, analyses molecular signatures in AML cancer cells to understand progression and/or therapy resistances.

Her group's research provides a foundation for novel personalised drug targets with the potential to maximise the benefit of current treatments and improve AML cure rates.

Transcriptome analysis of acute myeloid leukaemia cells

Technical situation

Dr Linda Holmfeldt, Principal Investigator in the department of Immunology, Genetics and Pathology at Uppsala University, used Qlucore Omics Explorer in a recent transcriptomic study to better understand the molecular characteristics of Relapsing/Primary Resistant (R/PR) Acute Myeloid Leukaemia patients.

Holmfeldt's group uses a combination of whole genome and/or exome sequencing, RNA sequencing, mass spectrometry analysis of the proteome as well as studies of the epigenome by DNA methylation microarrays. They also employ machine learning to generate hypotheses around tumour progression and/or therapy resistance.

Using these methods, they are building a more complete picture of DNA and RNA alterations in AML tumour cells, as well as their protein composition. Long term, the group hopes their findings may lead to treatment alternatives for high-risk R/PR AML patients.

Solution

In the past, finding sufficient samples from R/PR cases has been difficult. For the recent study (*Transcriptomic analysis reveals proinflammatory signatures associated with acute myeloid leukemia progression* by Svea Stratmann et al; **Blood Adv**. 2022) Holmfeldt's group was able to perform transcriptome-wide RNA sequencing on 70 relapsing or primary resistant AML patients (47 adult and 23 children) with known mutational background from samples held via Uppsala Biobank and Karolinska Institute Biobank, collected between 1995 and 2016.

"We started out looking at the RNA transcriptome, tracking back to mutations at the DNA level," says Holmfeldt. "Around that time, our bio-informaticist left! We had a license for Qlucore Omics Explorer's and had experimented with it, so it was the perfect time to try out the tool on our RNA-sequencing data."

Holmfeldt's group used Qlucore Omics Explorer for various pre-processing of the TMM-normalised data, including adjusting the data for gene length, carrying out log2 transformation separately for each conducted analysis (including different sets of samples), as well as performing batch correction.

"Thereafter, we used the software for differential gene expression analysis. We carried out PCA, hierarchical

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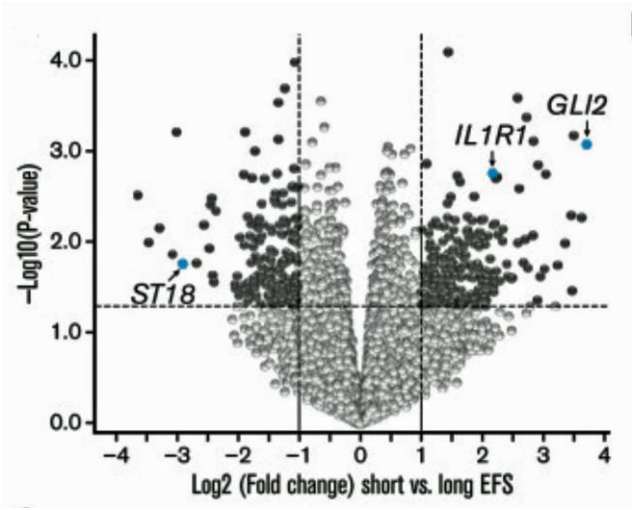

Above: Qlucore Volcano plot showing down-regulated ST18 (inhibitor) and up-regulated IL1R1 and GLI2 (pro-inflammatory) in AML, associated with short event-free survival.

clustering analysis, generated t-SNE- and Volcano plots as well as Venn diagrams," she explains.

They discovered a handful of genes of interest including CR1, DPEP1, GLI2, IL1R1, and ST18. "Within these, we identified CR1 down-regulation and DPEP1 up-regulation as specific for relapse in AML both for adults and children," she says.

The findings regarding GLI2, IL1R1, and ST18 were significant as they matched data from two other cohorts. They highlight the importance of a tumour-promoting inflammatory environment in leukaemia progression.

Benefits and future use

"Qlucore Omics Explorer is great because it allows users lacking a bioinformatics background to perform sophisticated analyses of large datasets, as well as to generate highly useful figures of publication quality," says Holmfeldt.

For the next project, her group will be using the same cohort at the proteome level. "We now have the transcriptomes from our entire AML cohort to use as a database to map our peptides to. We might be able to pick up novel leukaemia-specific peptides that come from regions previously thought to be untranslated," she says.

"In parallel, we will analyse the proteomics data in Qlucore again to look at what proteins are around at diagnosis compared to relapse. We hope that our findings may be used as biomarkers or as targets for immunotherapy. For proteomics analysis, we are very lucky to have Qlucore."

For More information

Contact Qlucore at www.qlucore .com.

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