Investigating resistance to IDH inhibitors in acute myeloid leukemia

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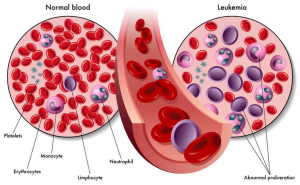
Summary



Acute Myeloid Leukemia is a blood cancer characterized by a blockage in myeloid differentiation and hyperproliferation of transformed myeloid progenitor cells.

The mutation in the gene isocitrate dehydrogenase 1 (**IDH1**) is implicated in Acute Myeloid Leukemia (**AML**), as cells with the alteration abnormally produce an oncometabolite 2-hydroxyglutarate (**2-HG**).

These IDH inhibitors have shown good clinical response in AML patients. However, primary or acquired **resistance to IDH inhibitor therapies** represent a major problem limiting their efficacy.

Methods

- Datasets
  - RNAseq (IDHi therapy) [**1**]
  - Affymetrix (Chemotherapy) [**2**]
- Data analysis
  - Differential gene expression (DEG)
  - Transcription factor activity inference (TFa) [**3**]
- Knowledge-based network
  - Protein-protein interaction [**4**]
  - Transcription factor - target genes
- Network analysis
  - Eigenvalue centrality

Results

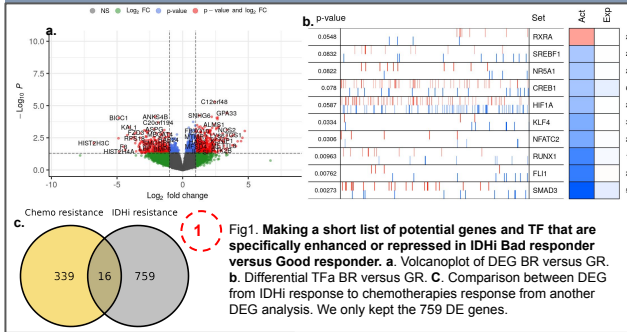
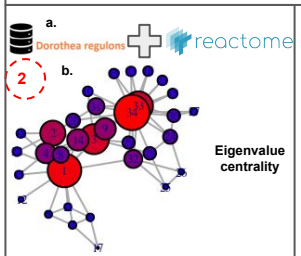


Fig1. **Making a short list of potential genes and TF that are specifically enhanced or repressed in IDHi Bad responder versus Good responder. a**. Volcanoplot of DEG BR versus GR. **b**. Differential TFa BR versus GR. **C**. Comparison between DEG from IDHi response to chemotherapies response from another DEG analysis. We only kept the 759 DE genes.



Eigenvalue measurement:

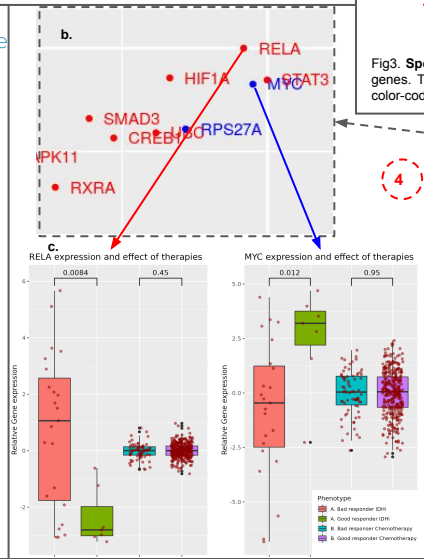
- Scale with number of connection to highly connected nodes in a directed graph

Page Rank:

- Eigenvalue centrality + Web search context (random jumps)

Node 34 is the most influential node in the network

Fig 2. **Construction and analysis of networks. a.** Merging of Dorothea Transcription factor - target genes with Reactom Functional Protein - Protein interaction networks **b.** Illustration of Eigenvalue centrality.



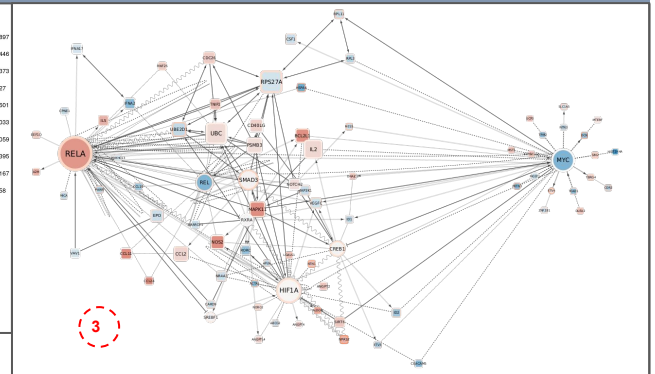


Fig3. **Specific IDHi resistance network.** Circles in the network correspond to TFs and squares are genes. The size of a node correspond to its eigenvalue centrality. Differential gene expression is color-coded from blue less expressed in BR to red more expressed in BR.

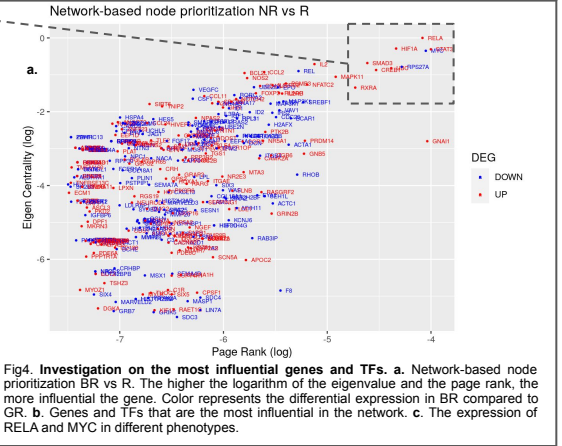


Fig4. **Investigation on the most influential genes and TFs. a.** Network-based node prioritization BR vs R. The higher the logarithm of the eigenvalue and the page rank, the more influential the gene. Color represents the differential expression in BR compared to GR. **b**. Genes and TFs that are the most influential in the network. **c**. The expression of RELA and MYC in different phenotypes.

Conclusion

From gene expression data and using **computational approaches**, we were able to highlight **potential key genes** of the resistance to IDH inhibitor therapies.

Transcriptional informations provide a **snapshot** of the current state of cells. From this snapshot we can still **infer transcription factor activity** to better fit to the reality and to investigate the master of the regulation in resistance.

The activity of TFs is linked to the gene expression and furthermore the **downstream activity of proteins**. Connections of targeted genes to other genes in a protein protein interaction manner help to **understand mechanisms in actions**.

Network analysis permits to focus attention on the **key effectors of the resistance**.

From this workflow **RELA** and **MYC** showed the highest interest and preliminary experiments in vitro are in progress to confirm this in silico result.

In addition, the network may **model the resistance** to IDHi inhibitor and may be the starting point of a method to **predict the response to the therapy**.

References

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