

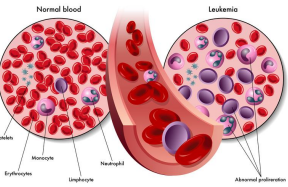
Investigating resistance to IDH inhibitors in acute myeloid leukemia

Alexis Hucteau¹, Nina Verstraete¹, Feng Wang², Courtney Dinardo², Koichi Takahashi², Vera Pancaldi¹ and Jean-Emmanuel Sarry¹

¹ Centre de recherche en Cancérologie de Toulouse (CRCT, UMR1037 Inserm / Université Toulouse III Paul Sabatier, Toulouse, France)

² The University of Texas MD Anderson Cancer Center (Houston, TX, United States)

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 (IDH1 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

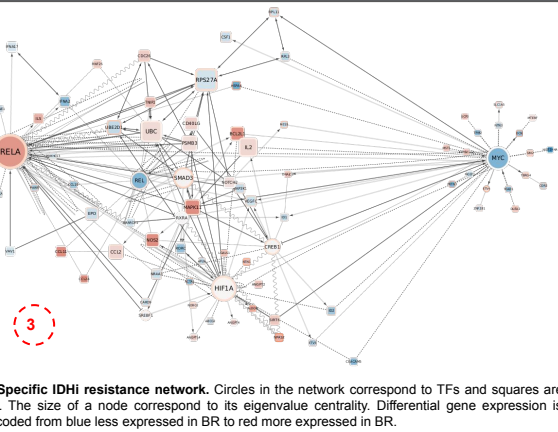
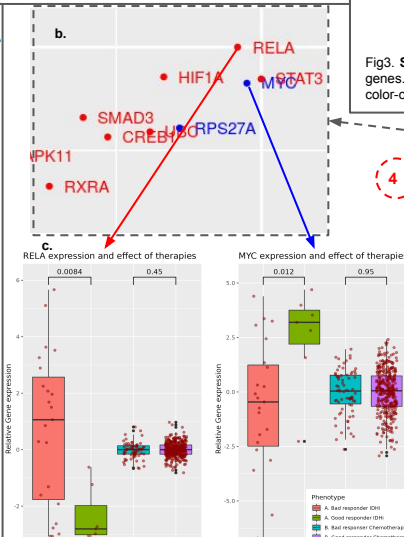
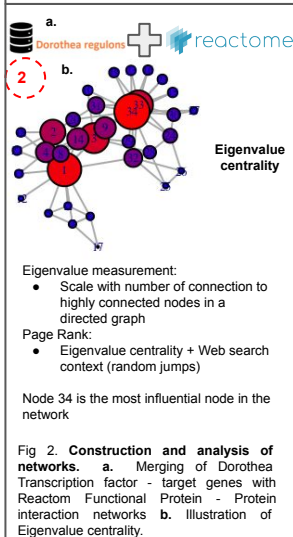
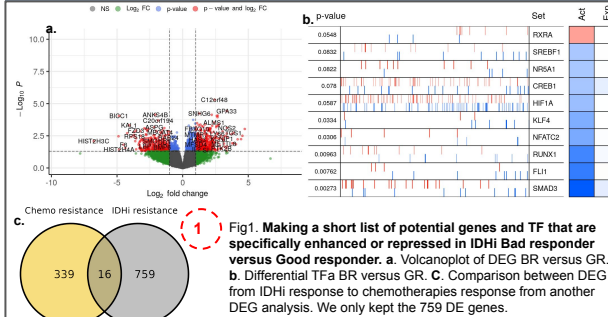


Fig4. Investigation on the most influential genes and TFs. a. Network-based node prioritization NR vs R. The higher the logarithm of the eigenvalue and the page rank, the more influential the gene. Color represents the differential expression in BR compared to GR. b. Genes and TFs that are the most influential 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 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 IDH1 inhibitor and may be the starting point of a method to **predict the response to the therapy**.

References

- [1] Feng Wang, Courtney Dinardo, Koichi Takahashi & al. Leukemia stemness and co-occurring mutations drive resistance to IDH inhibitors in acute myeloid leukemia. Nature Communication, 2021.
- [2] Verhaak RG, Wouters BJ, Eppelink CA, Abbas S et al. Prediction of molecular subtypes in acute myeloid leukemia based on gene expression profiling. Haematologica 2008.
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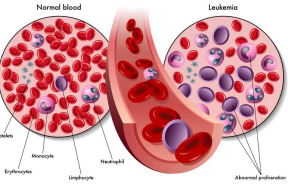
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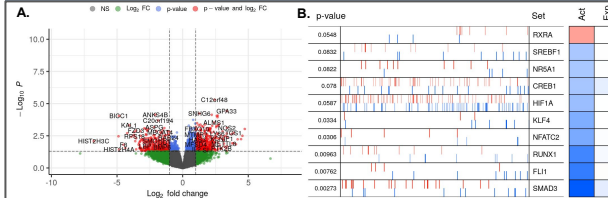


Fig1. Making a short list of potential genes and TF that are specifically enhanced or repressed in IDHi Bad responder versus Good responder. A. Volcanoplot of DEG BR versus GR. **B.** Differential TFa BR versus GR. **C.** Comparison between DEG from IDHi response to chemotherapies response from another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

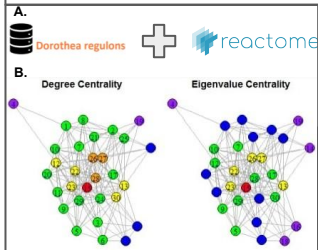


Fig2. Construction and measurement of the network. A. To better understand the pathway modified to resist to therapies, we aggregated two **knowledge-based network**: A transcription factor - target genes network called Dorothea and a functional Protein - Protein interaction network called Reactome. We only kept the 759 DE genes and the differentially active TF from the previous panel to build the network. **B.** To analyze the relevance of each node of the network, degree centrality correspond to the number of neighbor each node has but it doesn't take into account the are themselves highly connected or not. **Eigenvale centrality** is a measure of the influence of a node in a network as it looks at the value of the neighbor nodes.

Results

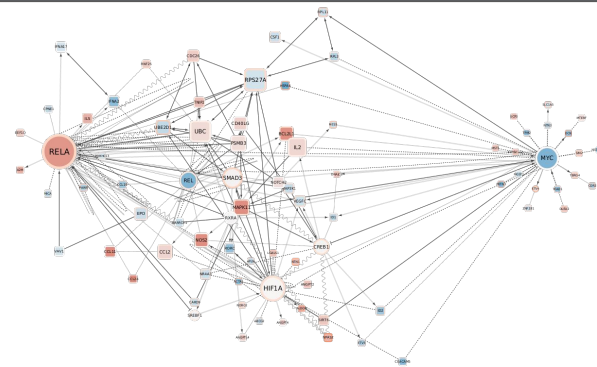


Fig3. Specific IDHi resistance network. Circles in the network correspond to TFs and squares are genes. The size of a node correspond to its eigenvale centrality. Differential gene expression is color-coded from blue less expressed in BR to red more expressed in BR.

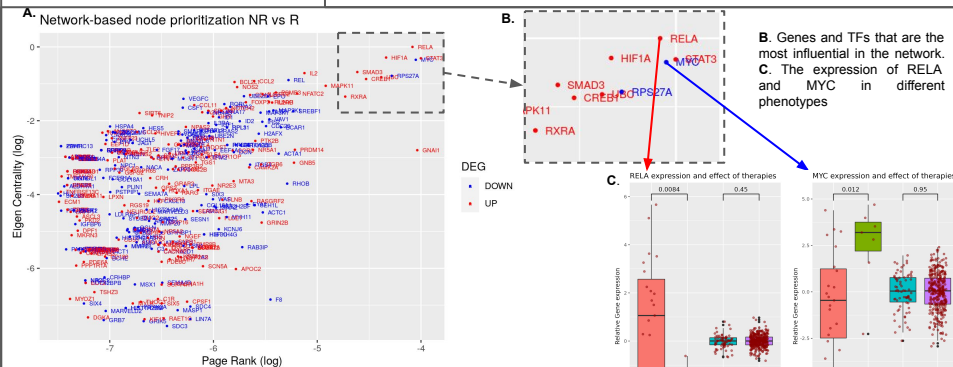


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Gene expression

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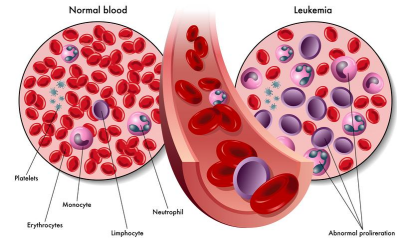
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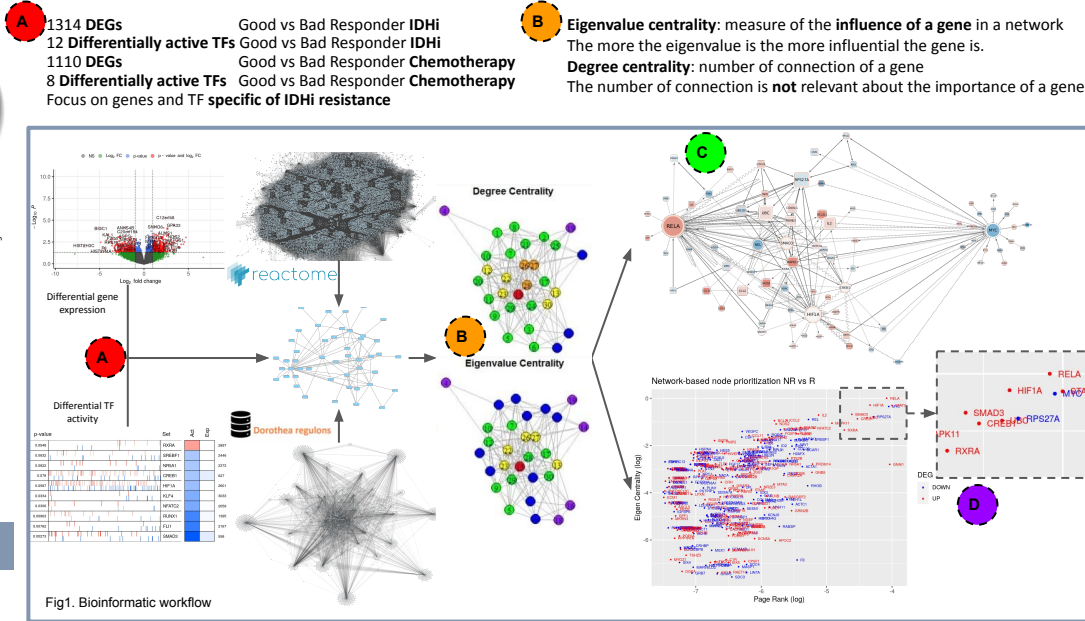
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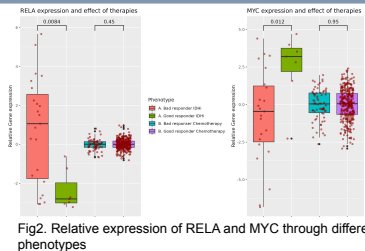
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Gene expression

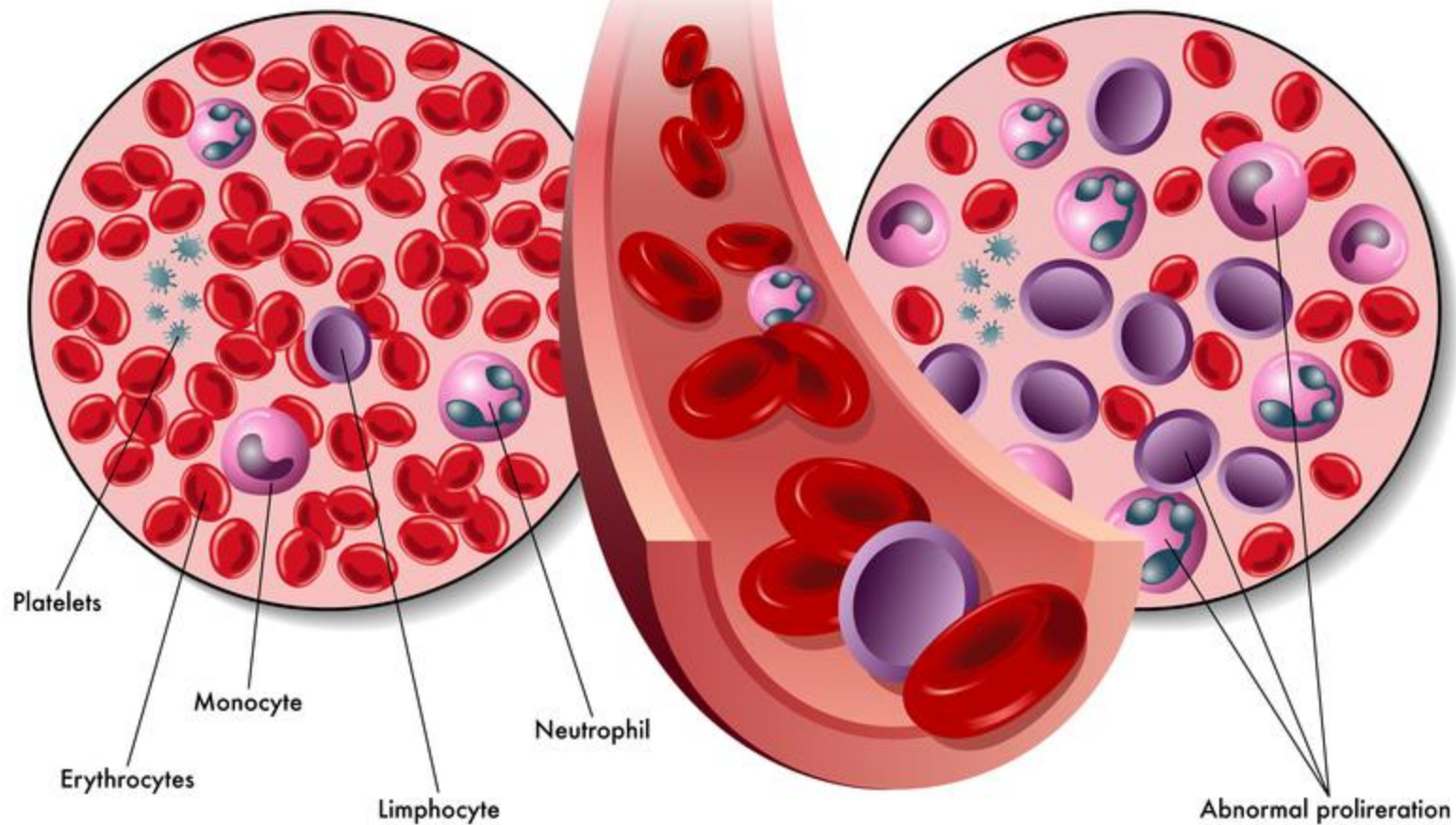


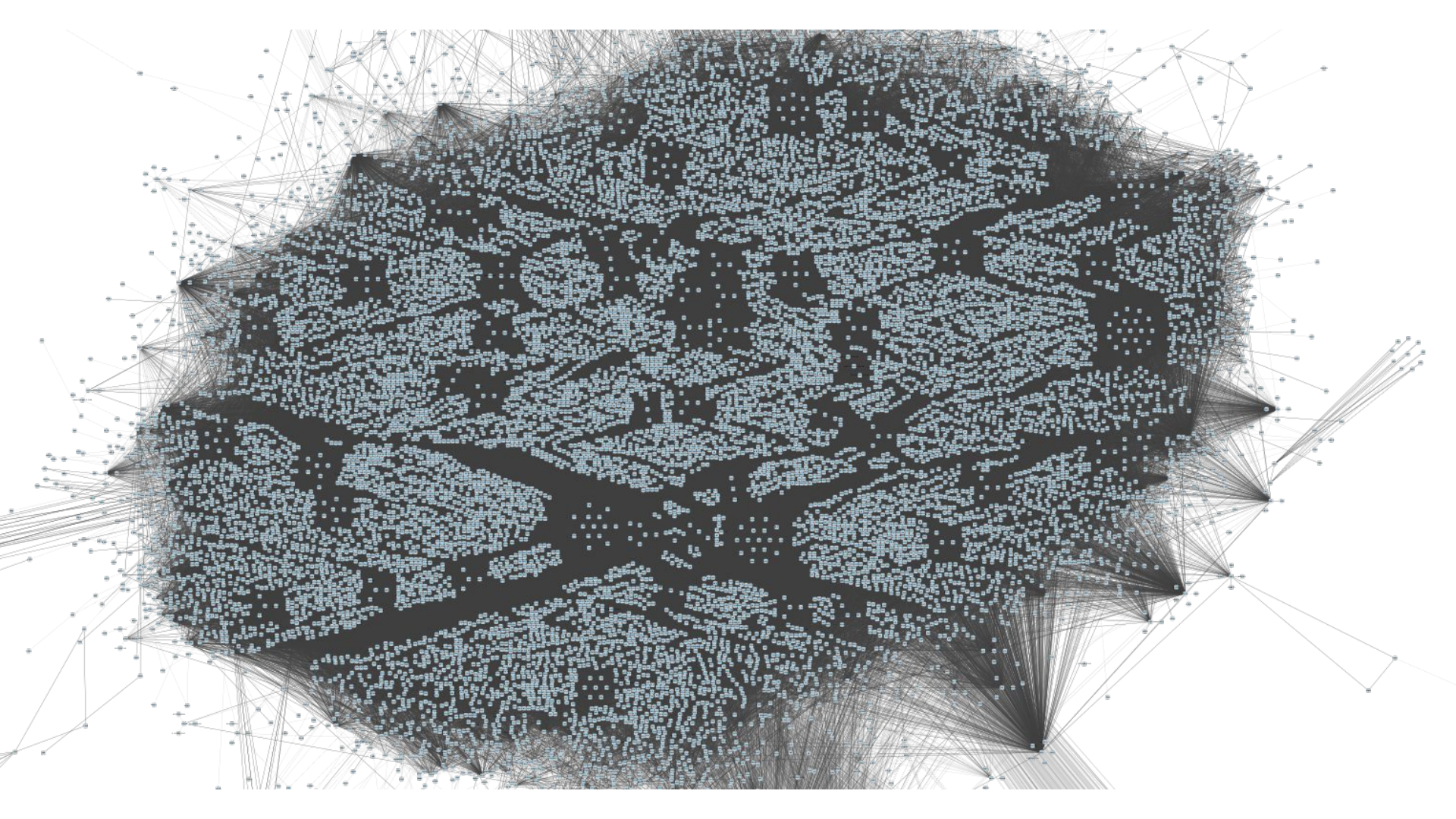
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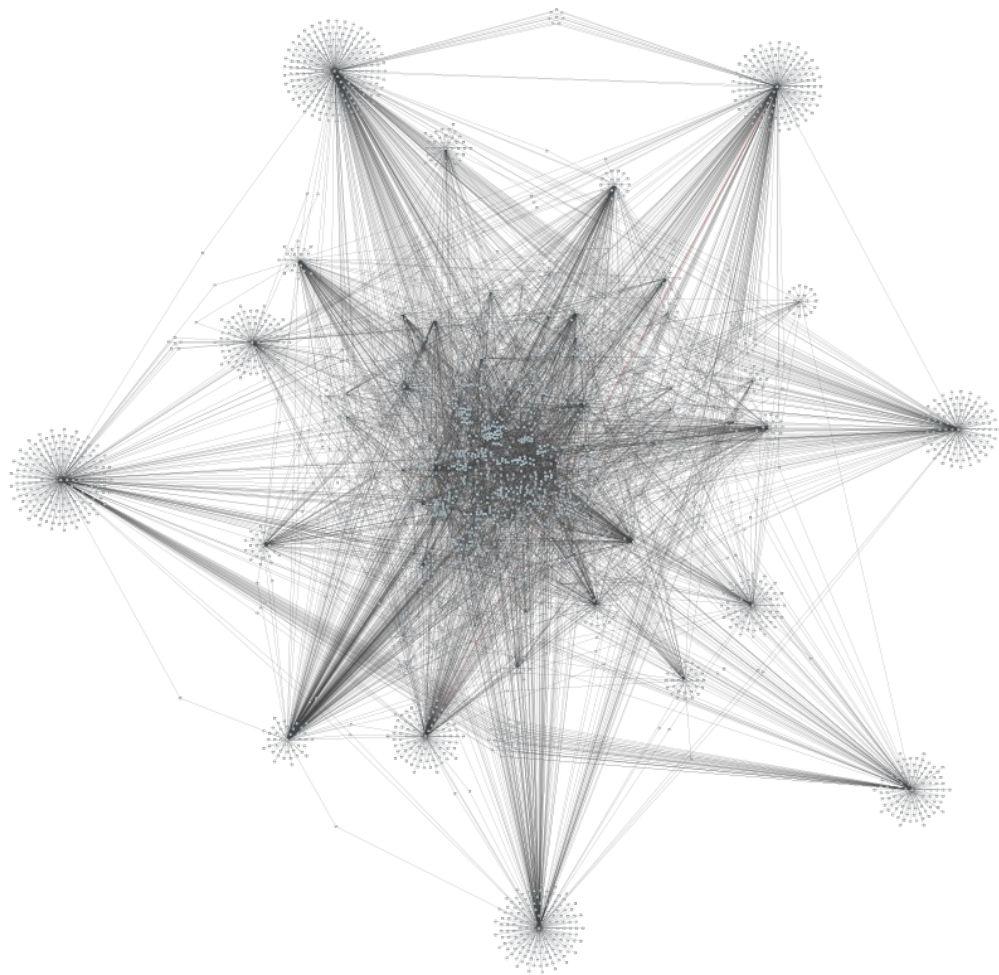
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Normal blood

Leukemia

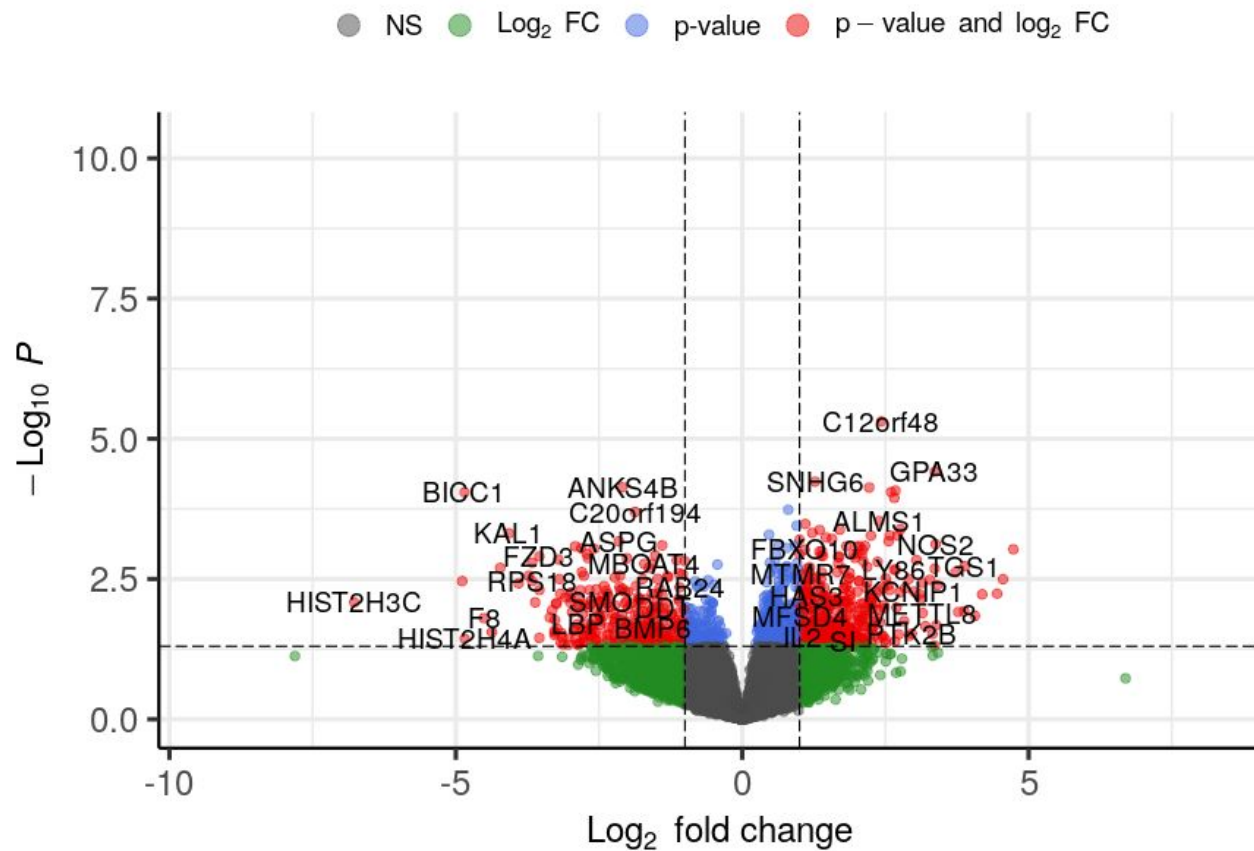




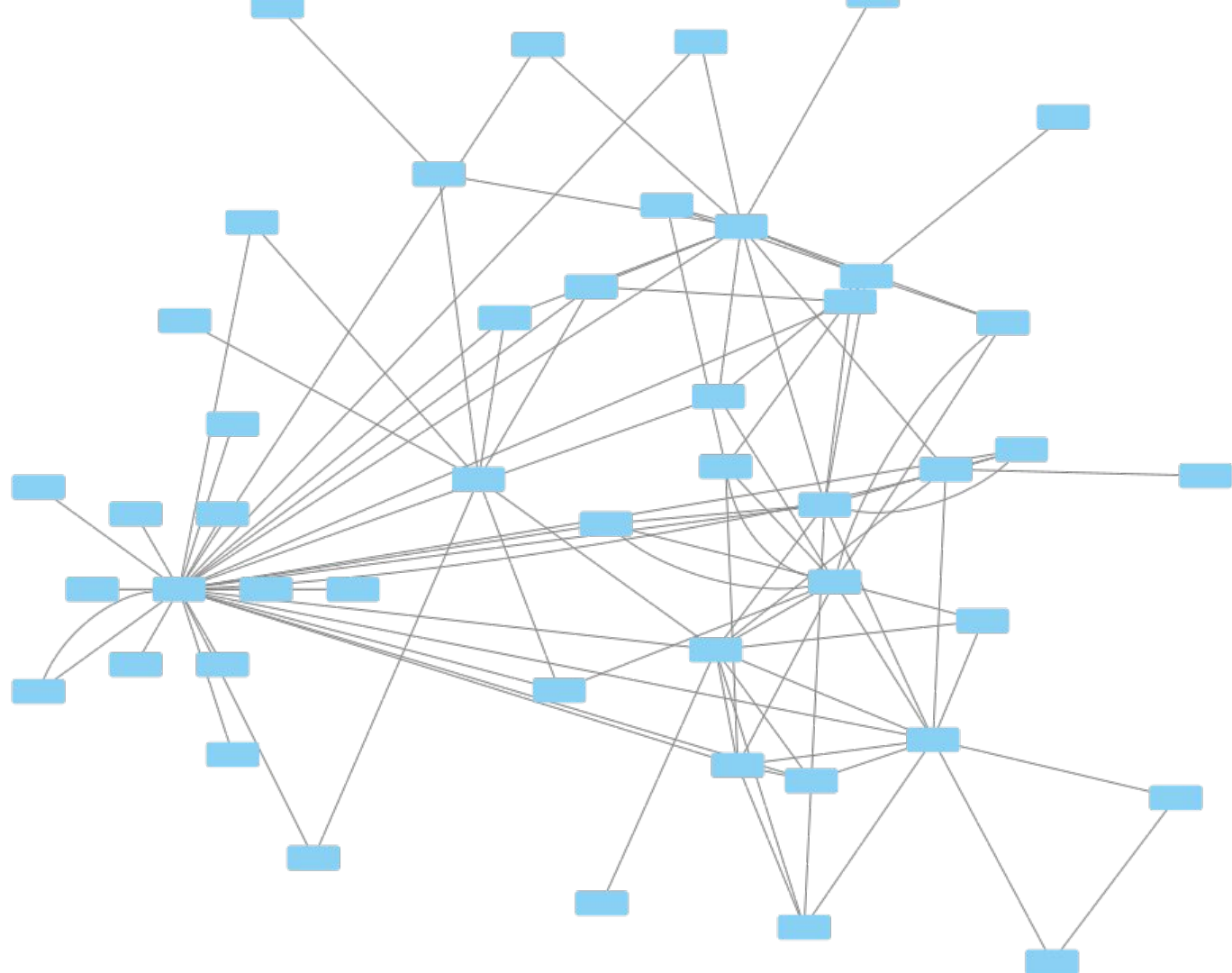


Volcano plot

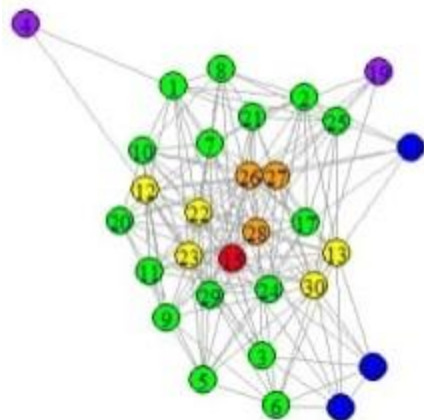
EnhancedVolcano



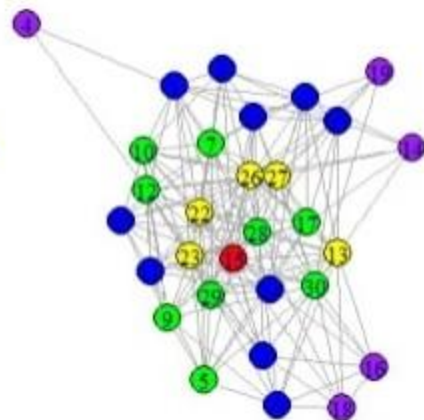
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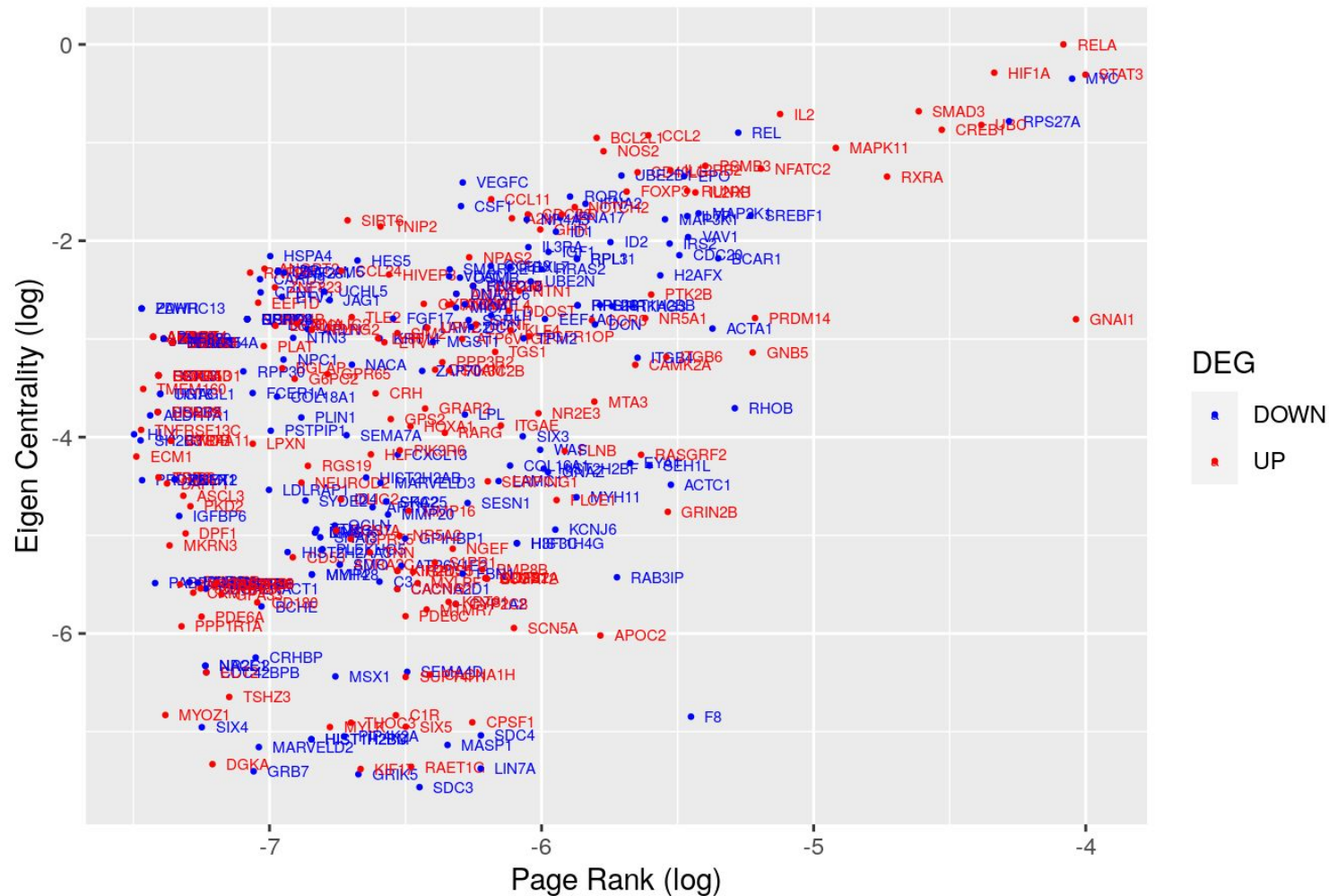
Degree Centrality

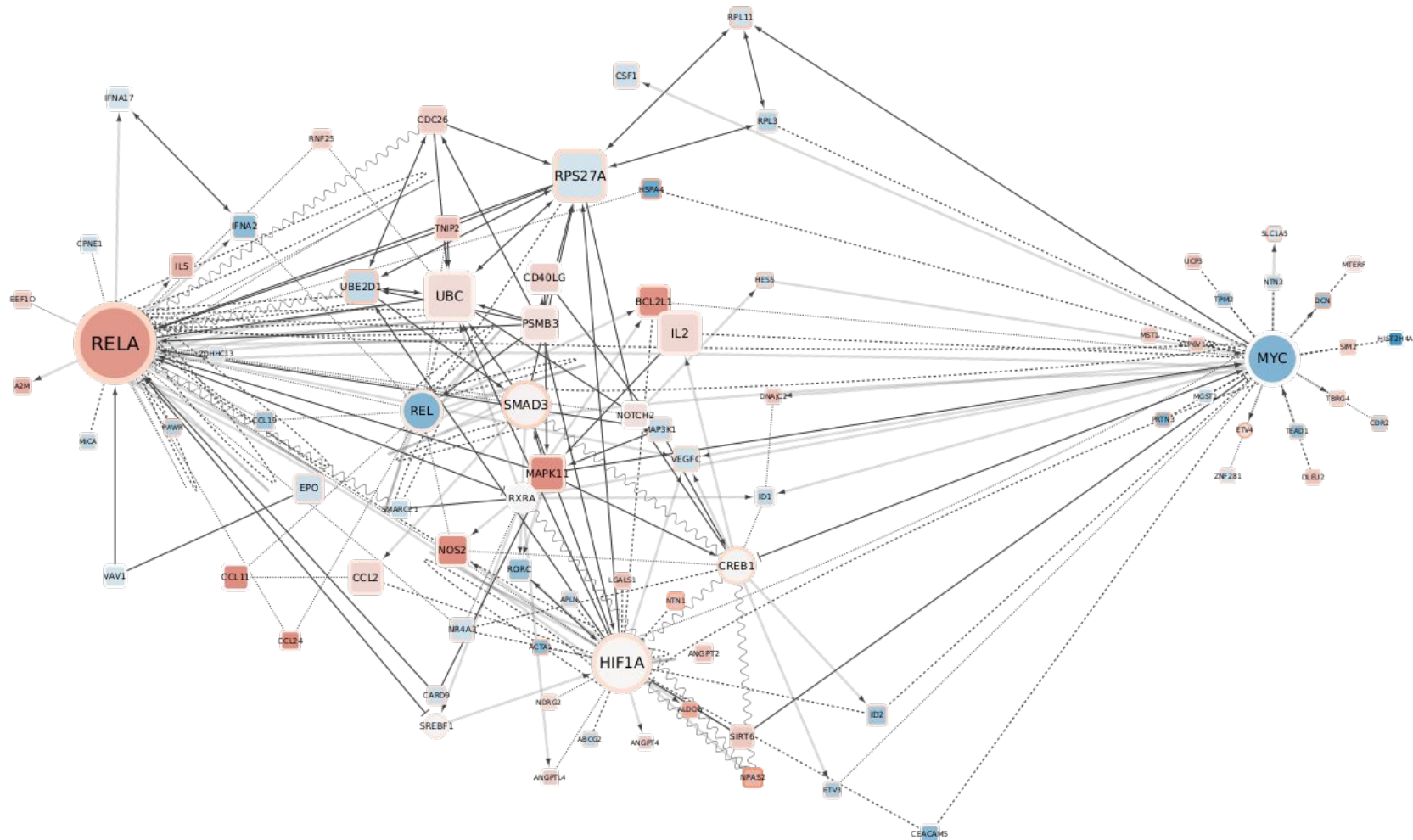


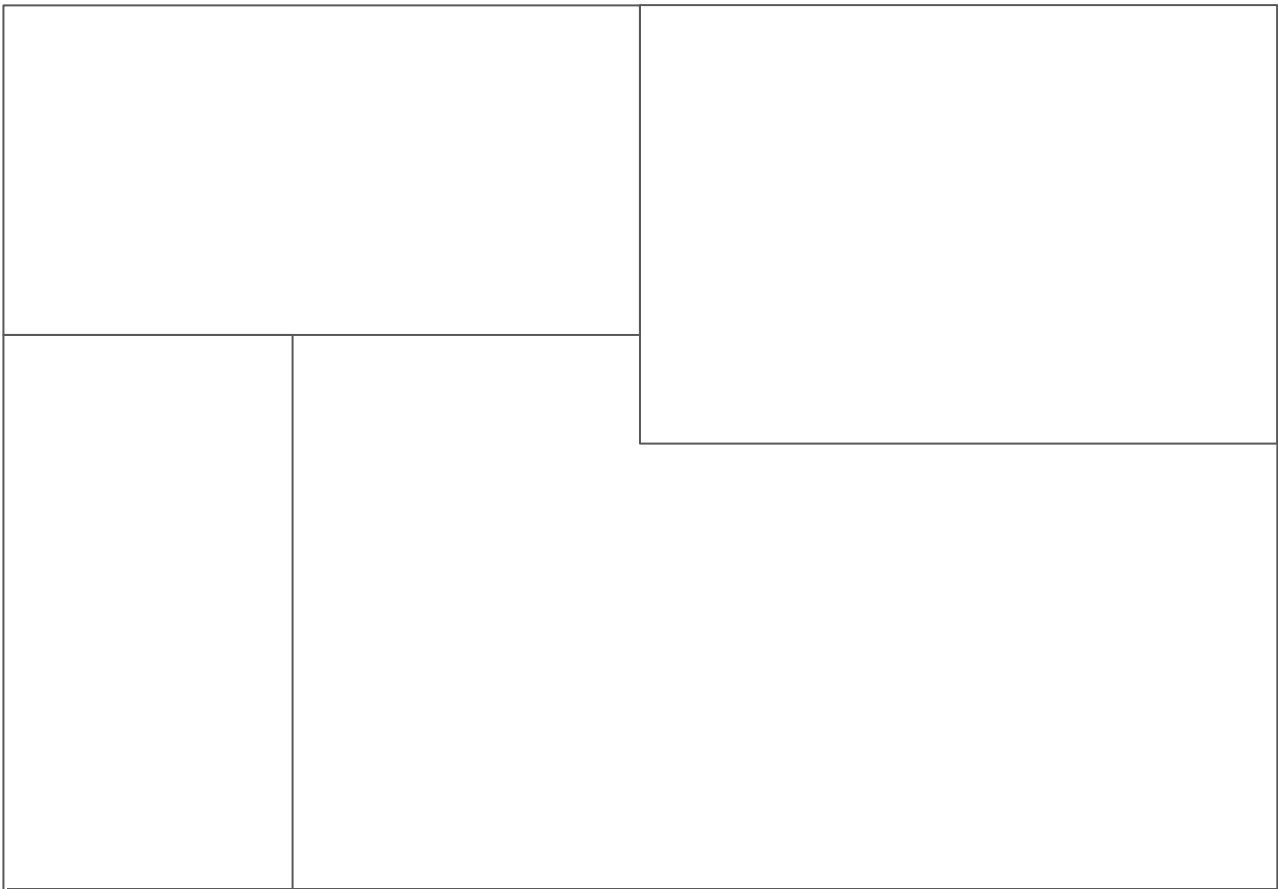
Eigenvalue Centrality



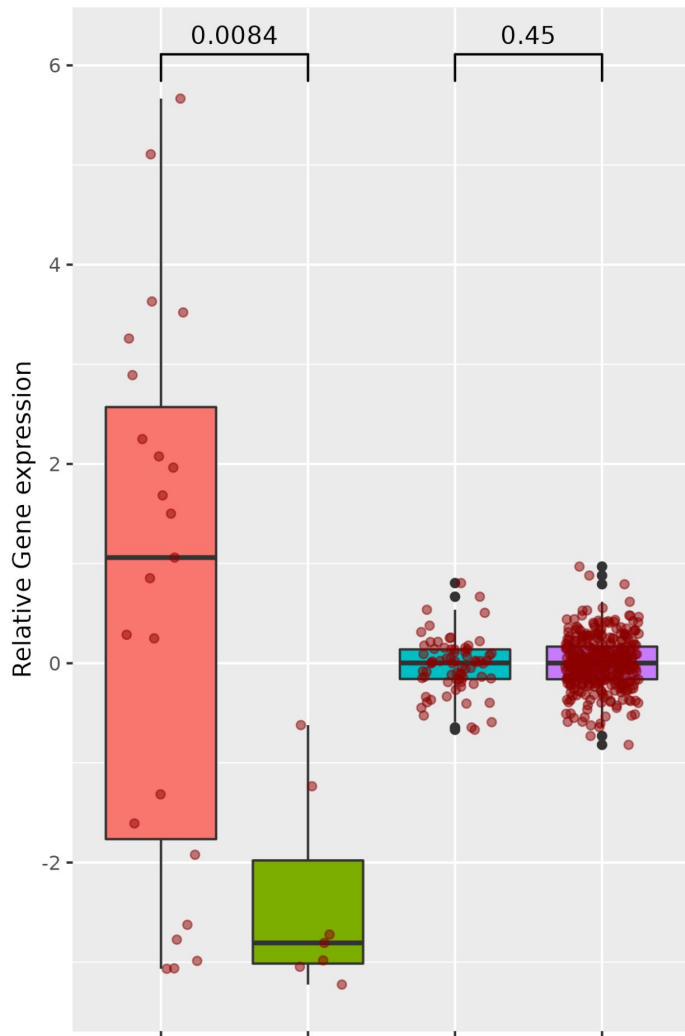
Network-based node prioritization NR vs R







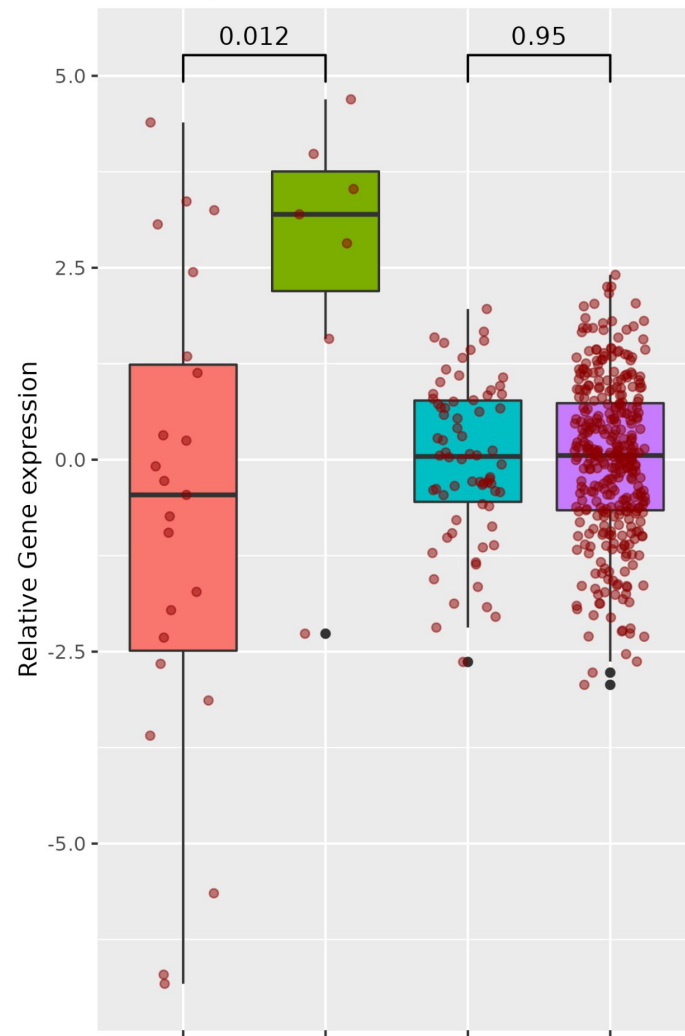
RELA expression and effect of therapies

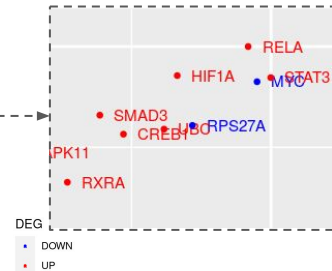
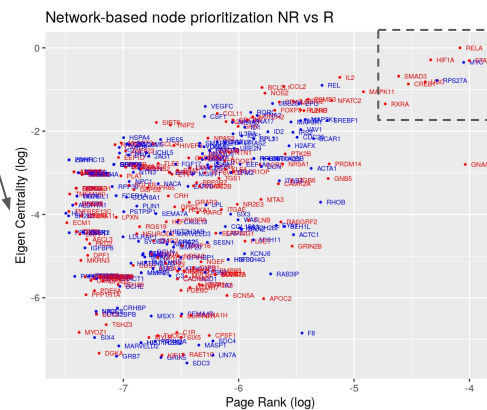
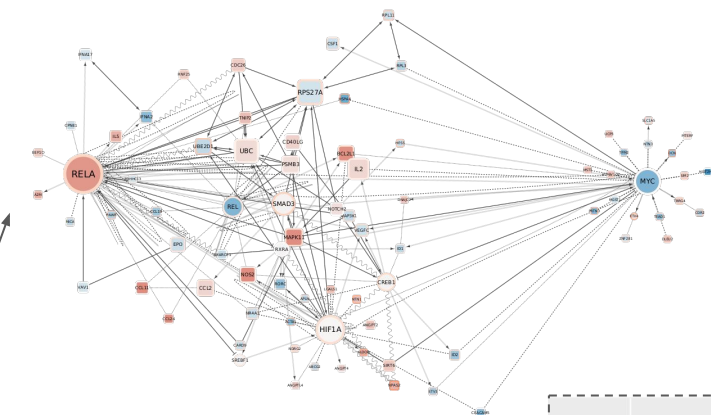
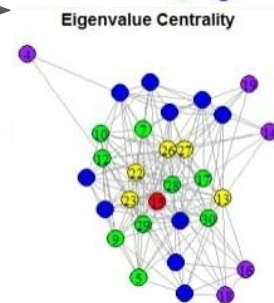
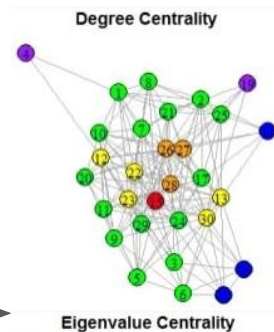
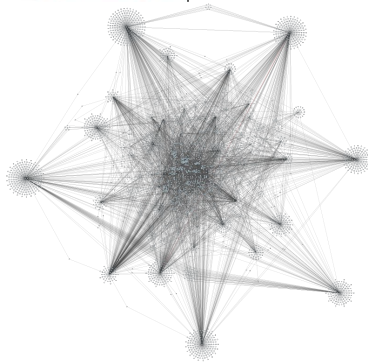
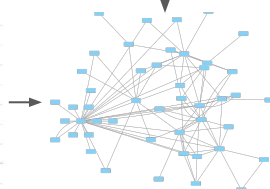
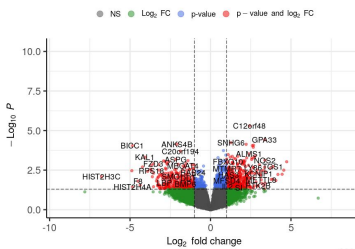


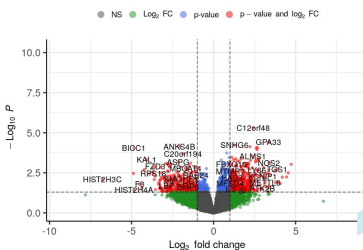
Phenotype

- A. Bad responder IDHi
- A. Good responder IDHi
- B. Bad responder Chemotherapy
- B. Good responder Chemotherapy

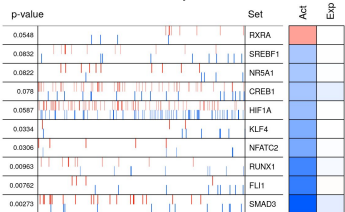
MYC expression and effect of therapies



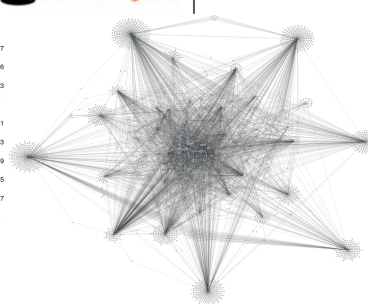




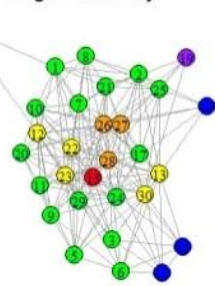
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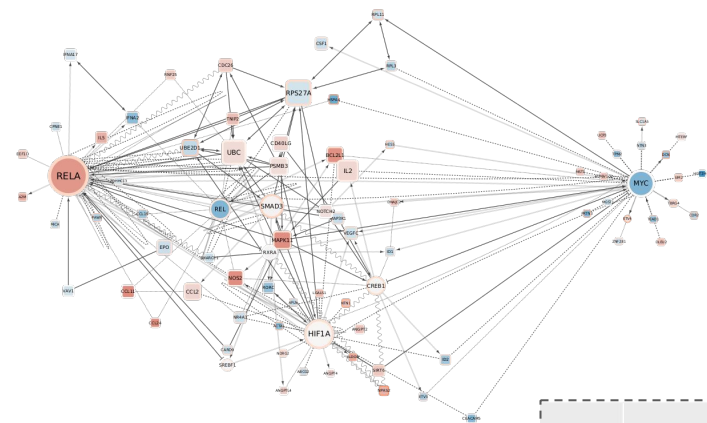
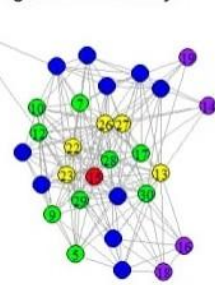
Dorothea regulons



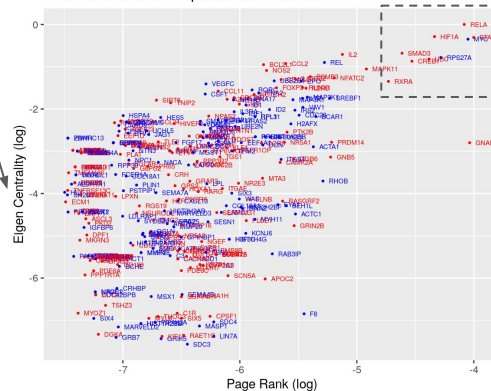
Degree Centrality



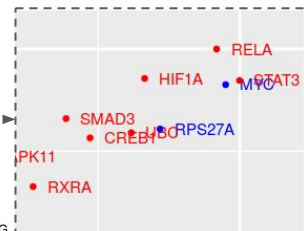
Eigenvalue Centrality



Network-based node prioritization NR vs R



DEG
● DOWN
● UP

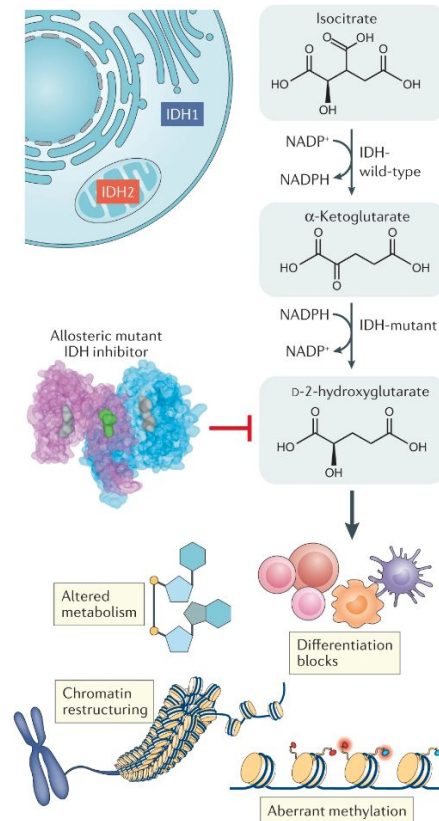
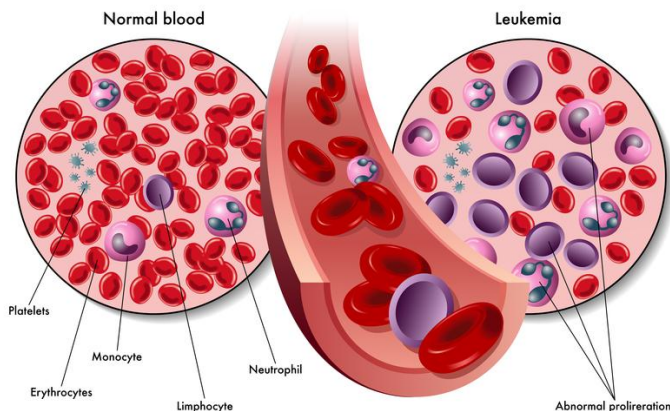


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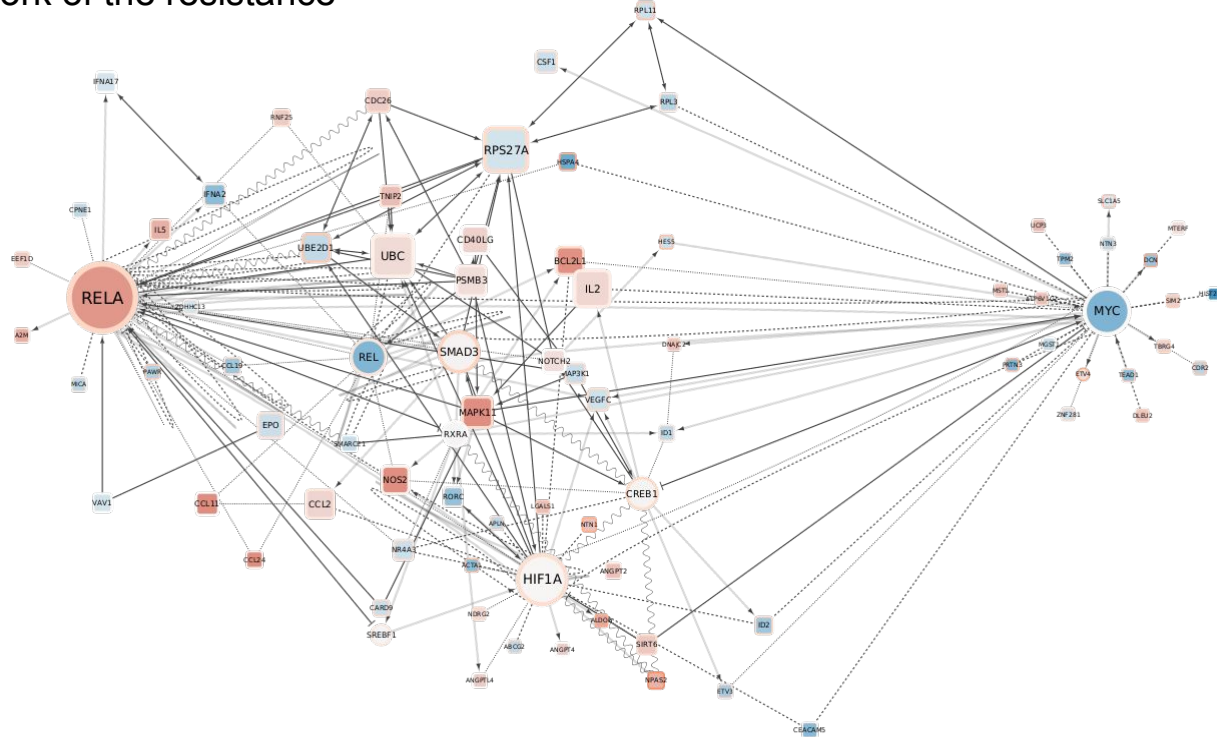
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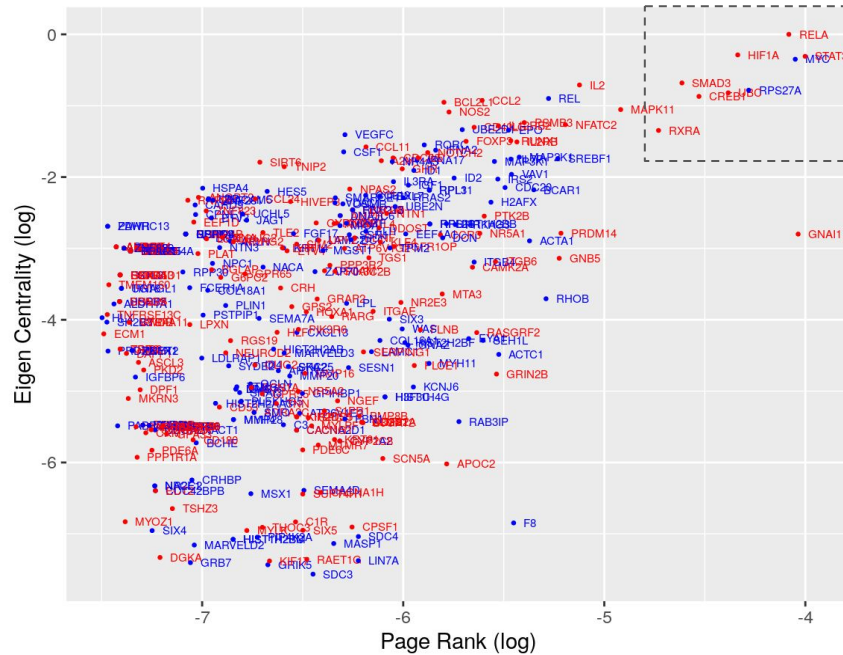
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- Specific Network of the resistance

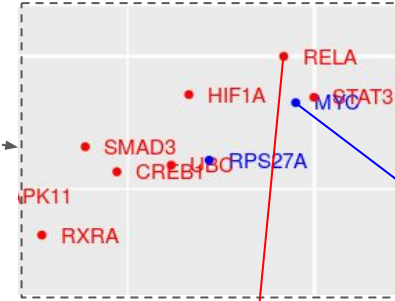


Network-based node prioritization BR vs GR

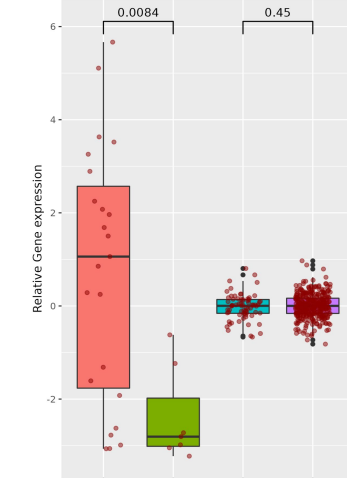


DEG

- DOWN
- UP



c. RELA expression and effect of therapies



MYC expression and effect of therapies

