A Big Data Analysis Platform Unveils the Gene Interactions in Cancer

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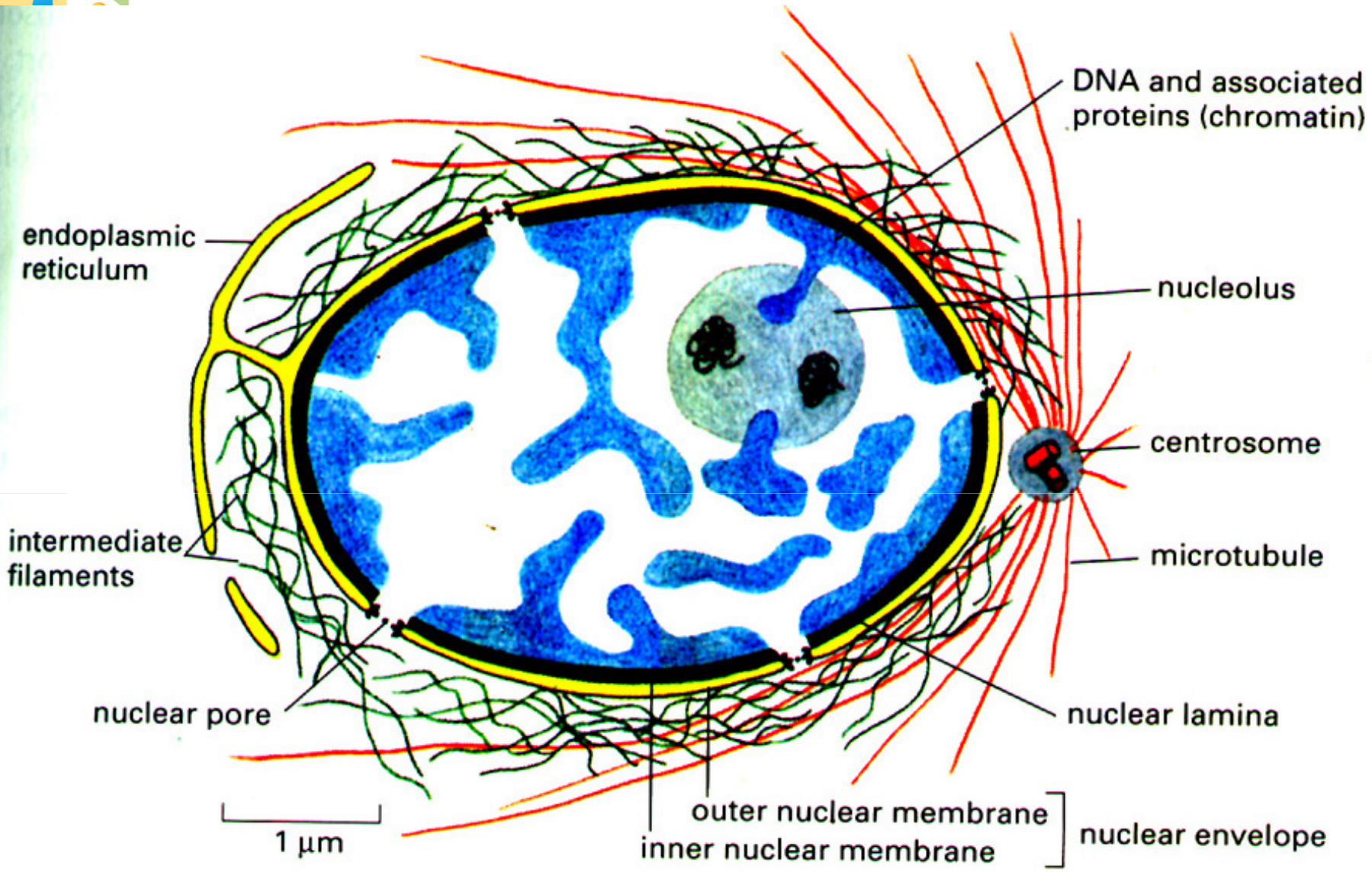
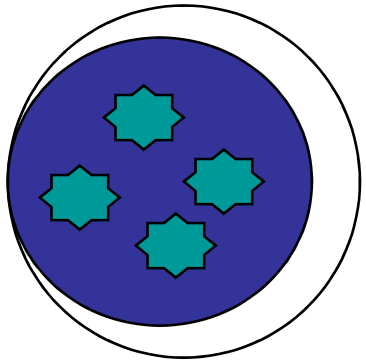

DNA and associated proteins (chromatin)
endoplasmic reticulum
nucleolus
centrosome
intermediate filaments
microtubule
nuclear pore
nuclear lamina
1 µm
outer nuclear membrane
inner nuclear membrane
nuclear envelope

Differences between cancer and normal cells

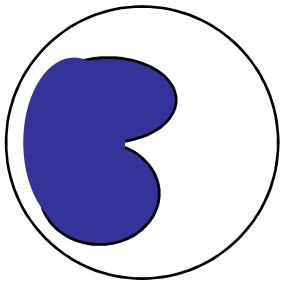
Cancer cells



Nucleolus

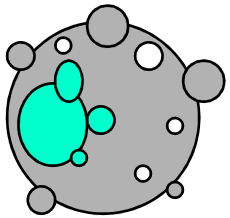
- Enlargement
- Pleomorphism
- Hyperactivity

Differentiated blood cells



No nucleolus

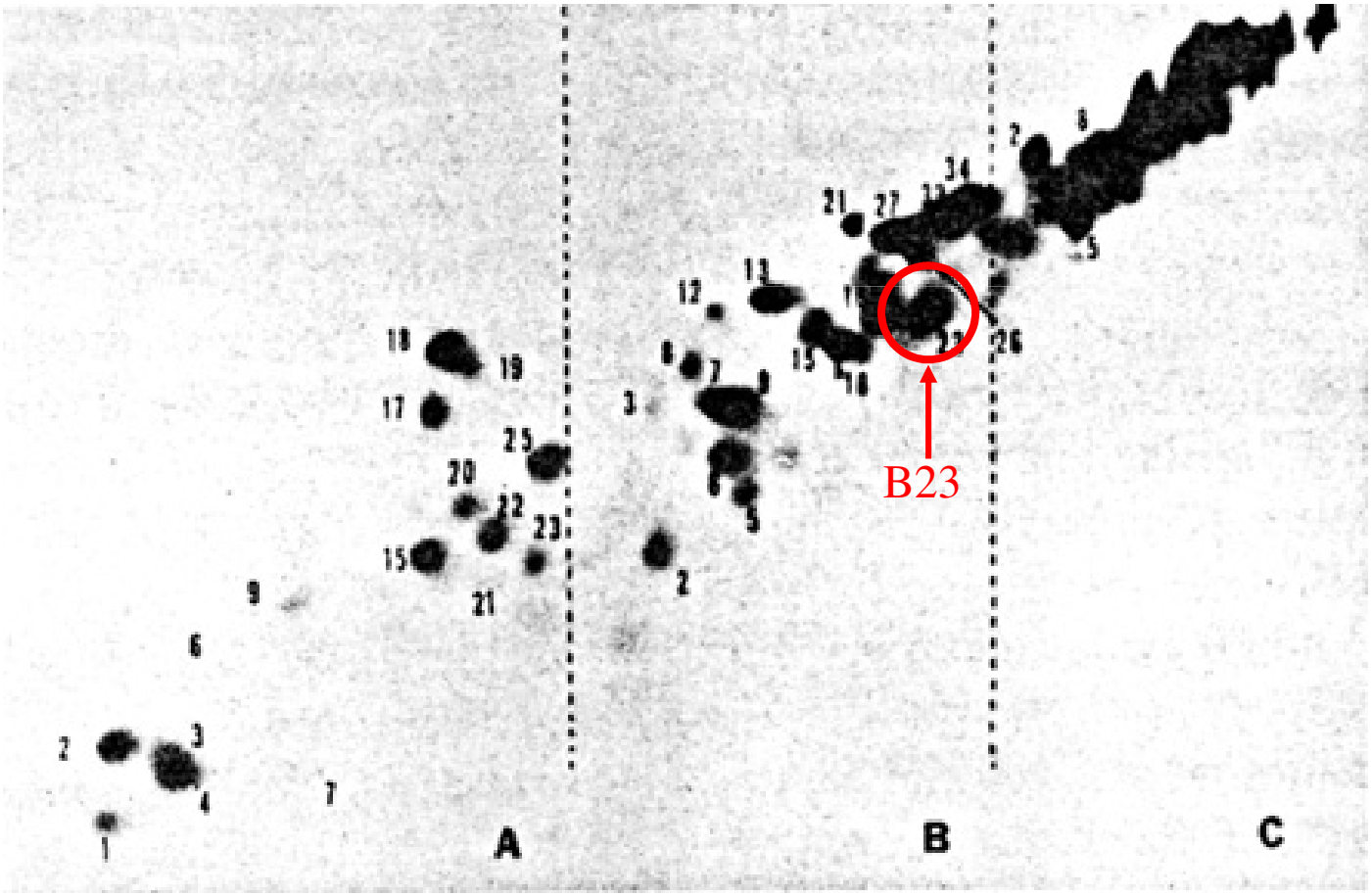
Apoptosis



2-D Gel Electrophoresis A, B, C Areas

10% acrylamide ,6 M Urea, 0.9N acetic acid →

SDS-PAGE ↓



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Nucleophosmin/B23 and Cancer

by Grisendi et al., Nature Reviews 6: 493-505 (2006)

Discuss how nucleophosmin/B23 could contribute to tumorigenesis.

B23 & Growth, Cell Cycle

Short exposure to actinomycin D induces "reversible" translocation of protein B23 as well as "reversible" inhibition of **cell growth & RNA synthesis** in HeLa cells.

Cancer Research 50:5987-5991 (1990)

Decreased accumulation and dephosphorylation of the mitosis-specific form Nucleophosmin/B23 in staurosporine-induced **chromosome decondensation**.

The Biochemical Journal 317: 321-327 (1996)

Down-regulation of nucleophosmin/B23 mRNA delays the entry of cells into **mitosis**.

BBRC 257:865-870 (1999)

Different kinases phosphorylate nucleophosmin/B23 at different sites during **G2 & M phases** of cell cycle.

Cancer Letters 153: 151-160 (2000)

NPM 1 & Differentiation, Apoptosis

Down-regulation of nucleophosmin/B23 during retinoic acid-induced differentiation of human promyeloicytic leukemia HL-60 cells.
Oncogene 16:915-924 (1998)

Mortalization of human promyelocytic leukemia HL-60 cells to be **more susceptible to sodium butyrate-induced apoptosis** and inhibition of telomerase activity by down-regulation of nucleophosmin/B23.
Oncogene 17:3055-3064 (1999)

Nucleophosmin/B23 regulates the susceptibility of human leukemia HL-60 cells to sodium butyrate-induced apoptosis and inhibition of telomerase activity. *Int. J. of Cancer* 83: 765-771 (1999)

Over-expression of nucleophosmin/B23 decreases **the susceptibility of** human leukemia HL-60 cells to retinoic acid-induced **differentiation & apoptosis.** *Int. J. of Cancer* 88: 392-400 (2000)

NPM 1 & DNA Damage, Repair, PCNA

Involvement of nucleophosmin/B23 in the **response** of HeLa cells to UV irradiation.

Int. J. of Cancer 97: 297-305 (2002)

Resistance to UV-induced cell-killing in nucleophosmin/B23 over-expressed NIH-3T3 fibroblasts: enhancement of **DNA repair and up-regulation of PCNA** in association with nucleophosmin/B23 over-expression.

Carcinogenesis 1:93-100 (2002)

UV stimulation of nucleophosmin/B23 expression is an **immediate-early gene *response*** induced by **damaged DNA.**

The J. of Biological Chemistry 277: 48234-48240 (2002)

NPM 1 & Ras, c-myc, p53

Increased stability of nucleophosmin/B23 in antiapoptotic effect of **Ras** during serum deprivation.

Molecular Pharmacology 59: 38-45 (2001)

C-myc-mediated expression of nucleophosmin/B23 decreases during retinoic acid-induced differentiation of human leukemia HL-60 cells.

FEBS Letters 578:211-216 (2004)

Association of nucleophosmin/B23 mRNA expression with clinical outcome in patients with bladder carcinoma.

Urology 64: 839-844 (2004)

Nucleophosmin/B23-binding peptide inhibits tumor growth **and up-regulates transcriptional activity of p53**.

BBRC 333: 396-403 (2005)

NPM 1 & Transcription

Nucleophosmin/B23 regulates PCNA promoter through **YY1**.

BBRC 335: 826-831 (2005)

Ras-dependent recruitment of c-myc for transcriptional activation of nucleophosmin/B23 in highly malignant U1 bladder cancer cells.

Molecular Pharmacology 70:1443-1453 (2006)

Nucleophosmin/B23 regulates transcriptional activation of E2F1 via modulating the promoter binding of **NF-κB, E2F1 and pRB**.

Cellular Signaling 18:2041-2048 (2006)

Nucleophosmin acts as a novel **AP-2α-binding** transcriptional co-repressor during cell differentiation. *EMBO Reports 8:394-400* (2007)

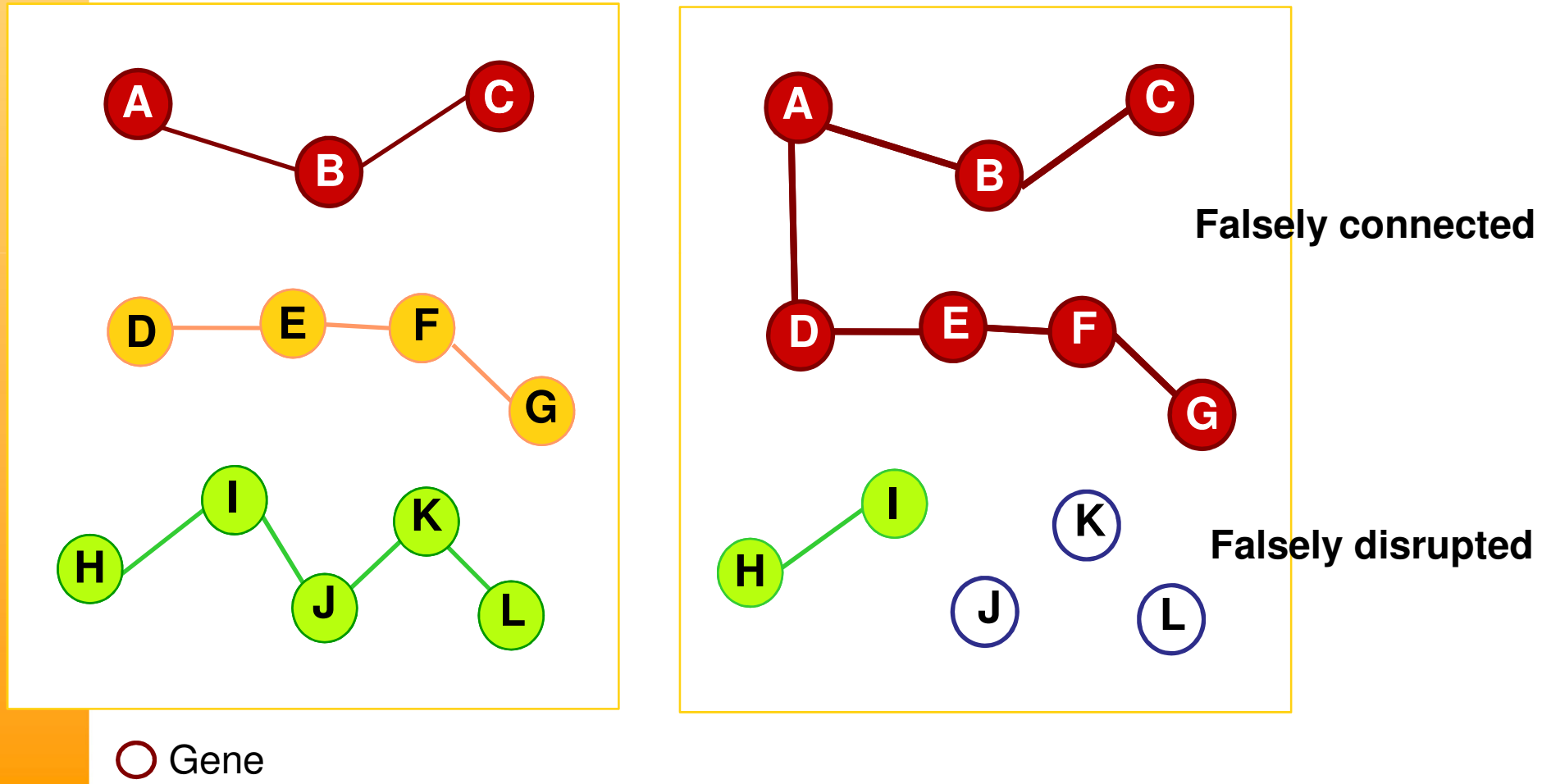
Dephosphorylation of nucleophosmin by **PP1β** facilitates **pRB binding** and consequent **E2F1-dependent DNA repair**. *Mol Biol Cell 21, 4409-17 (2011)*

Gene co-expression networks to investigate the inter-gene associations in expression profiles, reflecting functional linkages and potential coordinate regulations

The co-expression structure is defined as the distribution of co-expression levels for a group of genes over a state

Structural analysis seeks to identify a group of genes whose co-expression structure in one state (e.g., Neoplastic subjects) is significantly different from that in another state (e.g., normal)

Gene co-expression networks



Comparison of analytical method

Traditional method	PolyU big data analytics platform
20,000 genes	200,000,000 **gene pairs**
Quantify expression of individual genes	Quantify **gene interactions**
Differential expression of individual genes	Gene coexpression **network**

Gene co-expression networks

- Genome-wide
- Specific-gene oriented

  Nucleophosmin (NPM1) involved connections

NPM1

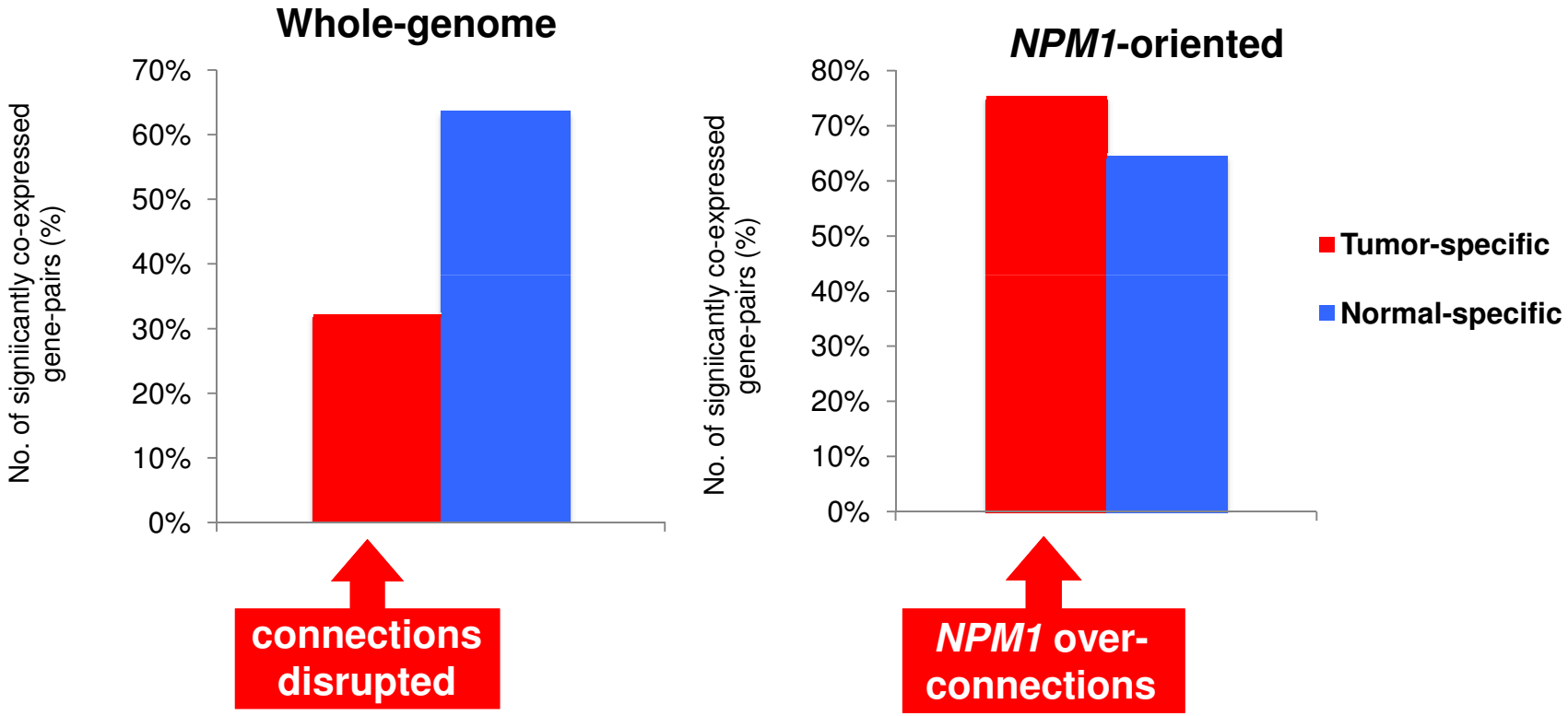
- Participate in many cellular processes

e.g. pre-ribosomal particles transport, **ribosome biogenesis**

- Critical in cell growth & proliferation control
- Frequently over-expressed/translocated in cancer

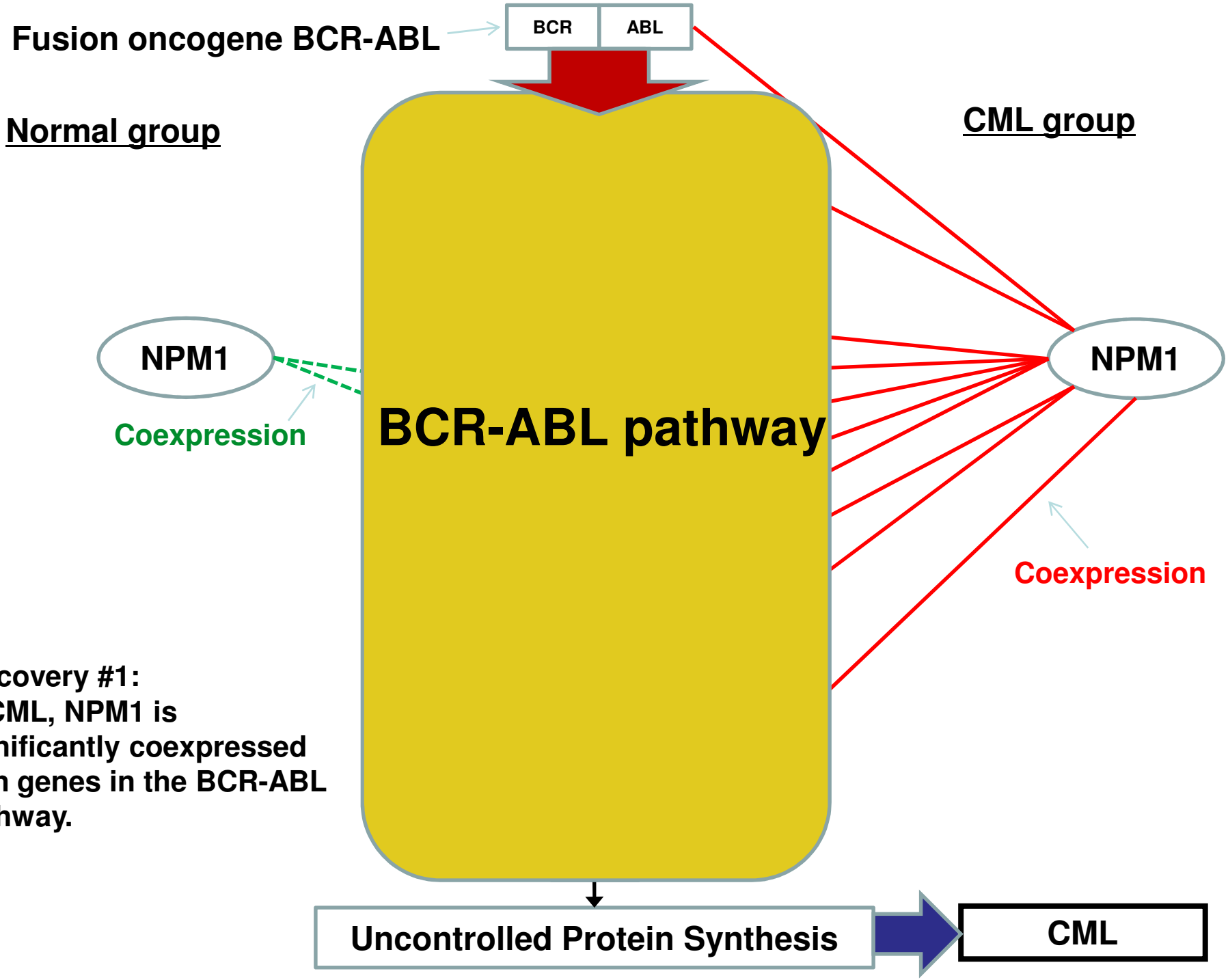
Gene co-expression networks

in Chronic Myelogenous Leukemia (CML)



NPM 1 responds to signals from MAPK, PI3K/AKT pathways initiated by oncogenic Ras

We quantified and compared the state-specific associations of NPM1 gene expressions from the combined BCR-ABL/MAPK/PI3K/AKT set of pathways

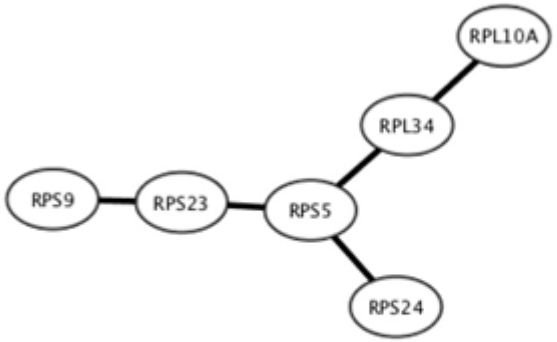

Fusion oncogene BCR-ABL
BCR
ABL
Normal group
CML group
NPM1
Coexpression
BCR-ABL pathway
NPM1
Coexpression
Discovery #1:
In CML, NPM1 is significantly coexpressed with genes in the BCR-ABL pathway.
Uncontrolled Protein Synthesis
CML

To further explore the role of NPM1 in ribosomal biogenesis, we analyzed the co-expression network of NPM1-associated genes in the Molecular Signature Database as a gene cluster covering most of the ribosomal proteins

Normal group

NPM1

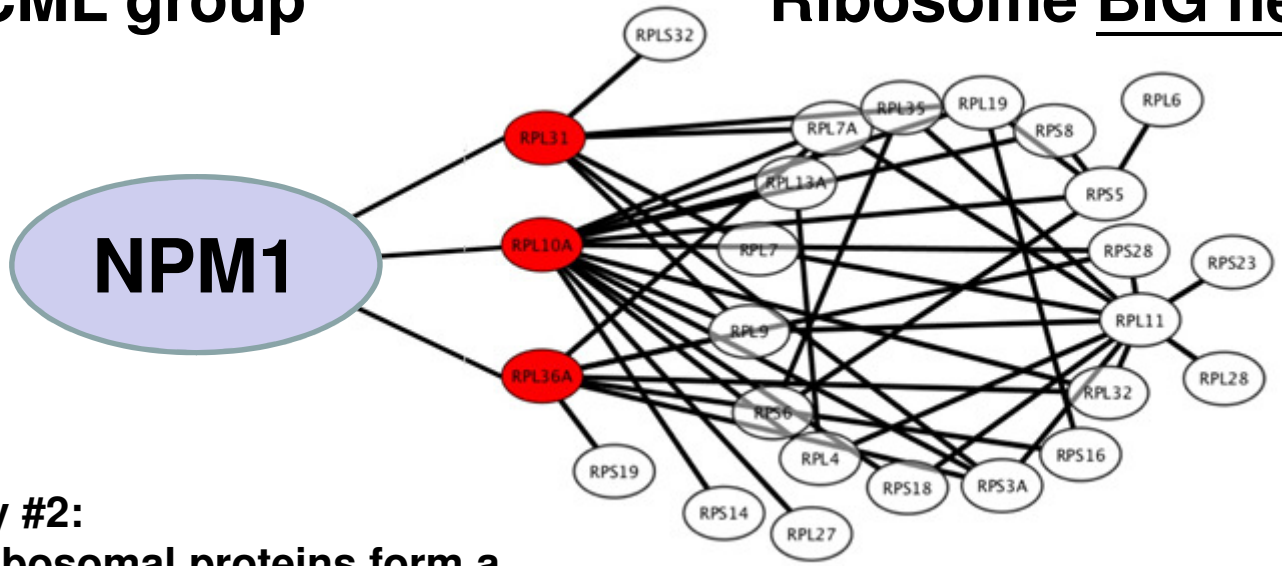
Ribosome small network



CML group

NPM1

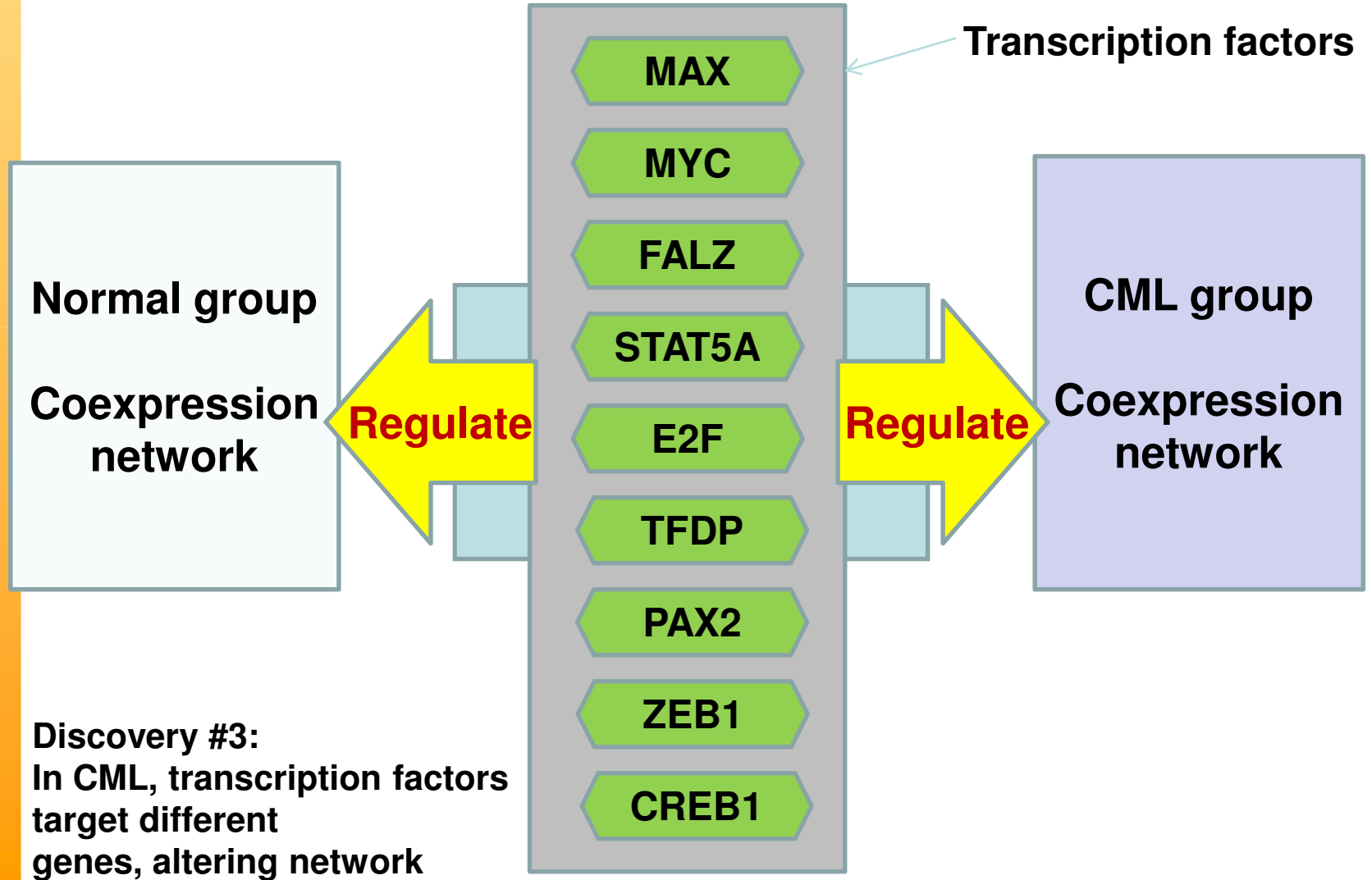
Ribosome BIG network



Discovery #2:
In CML, ribosomal proteins form a big network linked to NPM1.

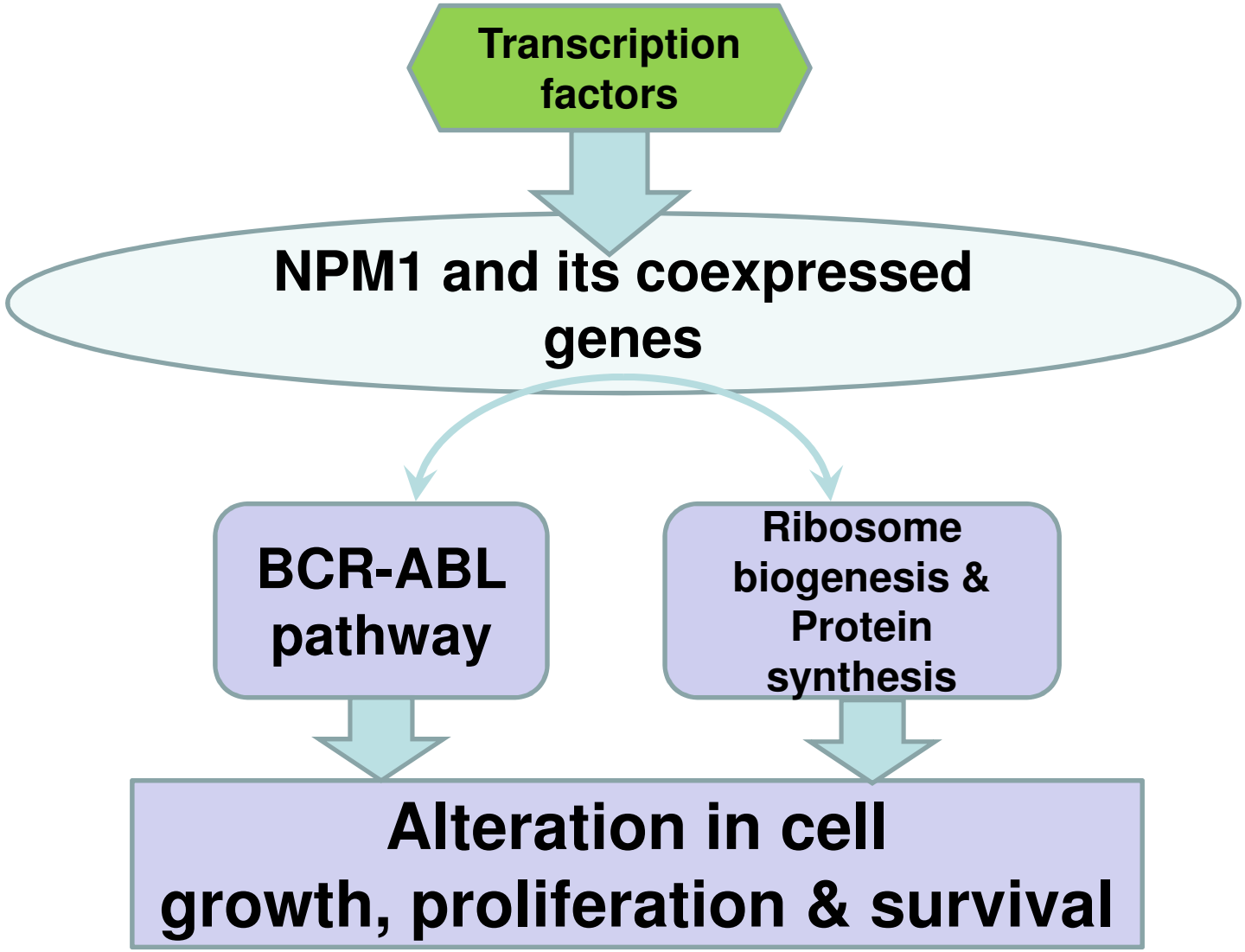
Using the Prediction of Transcriptional Regulatory Modules database, we identified transcription factors that concurrently target the NPM-doublets and elucidated their effects on co-expression patterns

Control of Coexpression through Transcription factors



Discovery #3:
In CML, transcription factors target different genes, altering network links.

Summary of Research Findings



Significance of research finding

Established a novel structural co-expression network analysis: enables us to unveil cancer pathogenesis and its **potential NPM1-oriented treatment strategy in CML.**

Co-expression analysis discovers **novel unregulated patterns of gene network** for understanding cancer biology, identifying new targets for treatment and all these innovations contribute to great science after all.

Targeted therapy can become more targeted after knowing the gene interactions, co-expressions, the transcription factors and pathways.

This platform can **readily be applied to other diseases** for diagnostic, prognostic and therapeutic investigation.

Cross disciplinary collaboration has enabled the team **to unveil cancer pathogenesis with expertise in biostatistics, pathology and biochemistry.**

Significance of research finding

Our Big Data Analytics Platform:

Analyze the interactions of 200,000,000 gene pairs … in few days

Traditional method:

Perform 200,000,000 experiments … infeasible

Project team members:

PolyU

Prof Benjamin Yung (PC)
- Cancer biology, NPM1

Dr Lawrence Chan
- Bioinformatics, Co-expression model

Dr Cesar Wong
- Cancer genomics, biomarker development

Dr Parco Siu
- Metabolic syndromes

HKUST Prof King-Lau Chow
- Functional genomics

CUHK Prof Anthony Chan
- Clinical oncologist

Prof Simon Ng
- Surgeon

Prof Benny Zee
- Bioinformatics

International Collaborators

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- Biostatistics

Dr Andrea Baccarelli
Havard School of Public Health
- Environmental epigenetics


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PolyU develops big data analysis platform to analyze gene interactions in cancer
理大研發大數據平台分析致癌基因關係
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翁一鳴教授
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Thank you