

Transcription Factors

MYC-mediated transcriptional programs and oncogenic growth

Mechanisms • molecular pathology • clinicopathologic reasoning

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

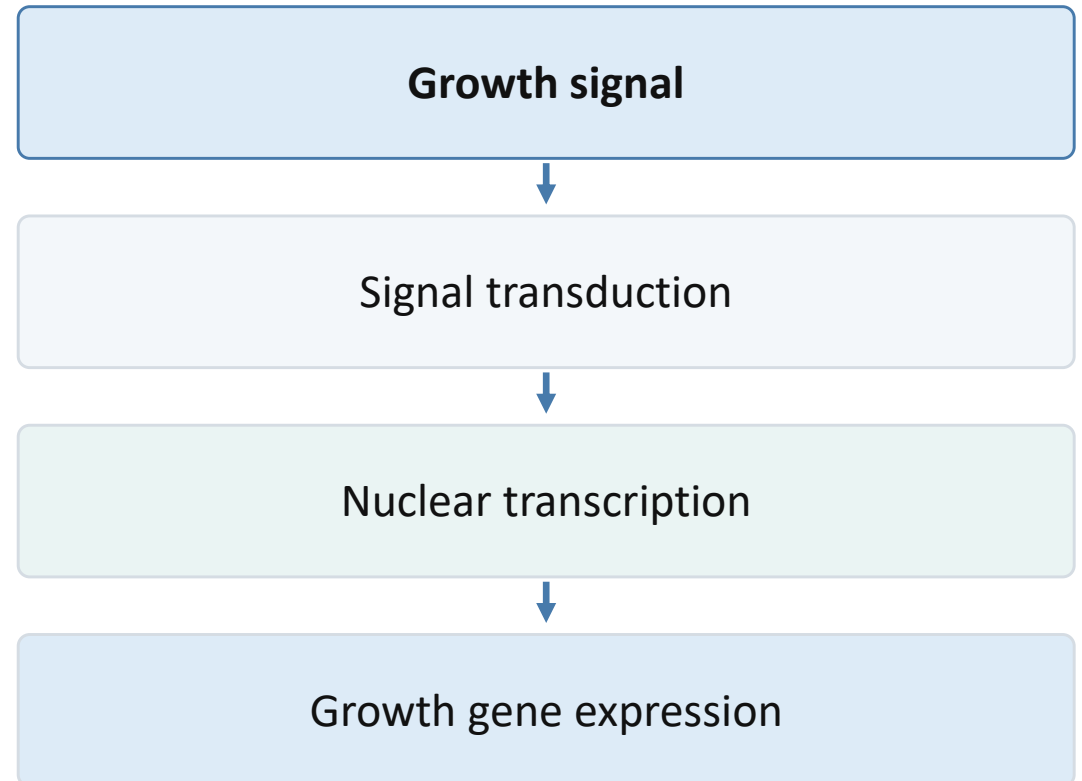
www.abusuraihsakhri.com

Lecture objectives

- Explain how mitogenic signals converge on nuclear transcription factors.
- Describe MYC regulation and the major MYC-dependent growth programs.
- Distinguish MYC translocation, amplification and pathway-mediated activation.
- Interpret cancer examples without confusing a molecular mechanism with a diagnostic test.

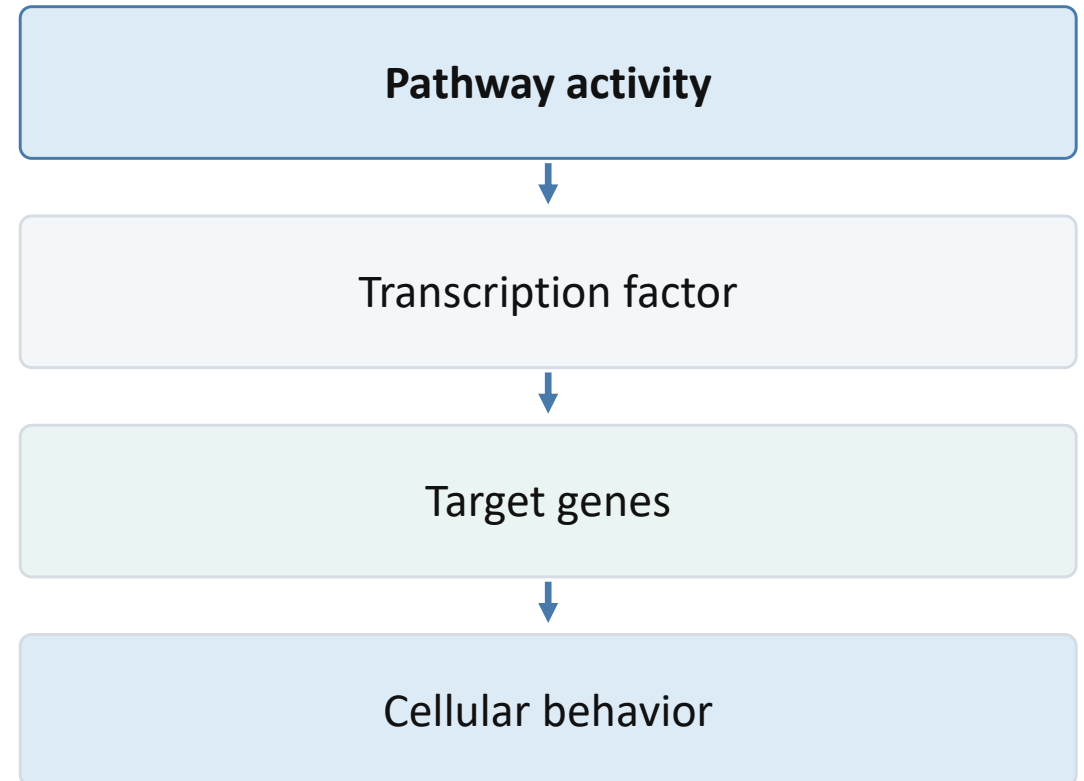
A nuclear endpoint for mitogenic signaling

- Growth factors activate signaling cascades that ultimately change gene expression.
- Transcription factors translate signal activation into a nuclear growth program.
- Continuous signaling can persistently activate growth-promoting genes.



Transcription factors connect signals to phenotype

- A pathway becomes biologically consequential when target-gene transcription changes.
- The resulting proteins can control growth, division, survival and biosynthesis.
- Transcription factors form the functional link between upstream signaling and output.



Oncogenic change: Upstream versus nuclear

Upstream activation

Receptor or signaling component is deregulated.

A normal transcription factor may receive persistent input.

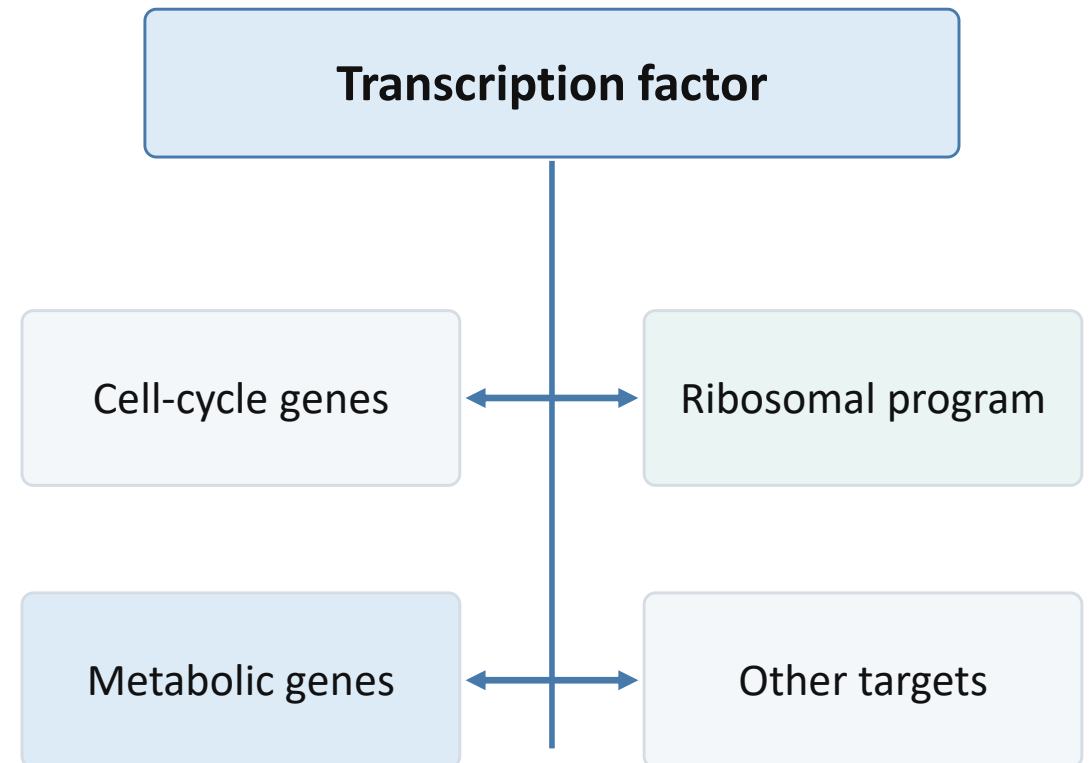
Nuclear activation

A transcription-factor gene itself can be altered.

The output program becomes excessive despite physiologic control.

A transcription factor can drive many target genes

- Some factors coordinate a narrow transcriptional program.
- Others regulate numerous genes with multiple functional consequences.
- MYC is emphasized because its effects are especially broad.



Transcription factors implicated in oncogenesis

- The supplied cancer chapter lists MYC, MYB, JUN, FOS and REL as proto-oncogenes.
- These genes encode transcriptional regulators of growth-associated programs.
- MYC is the most frequently dysregulated member highlighted in this section.

MYC

MYB

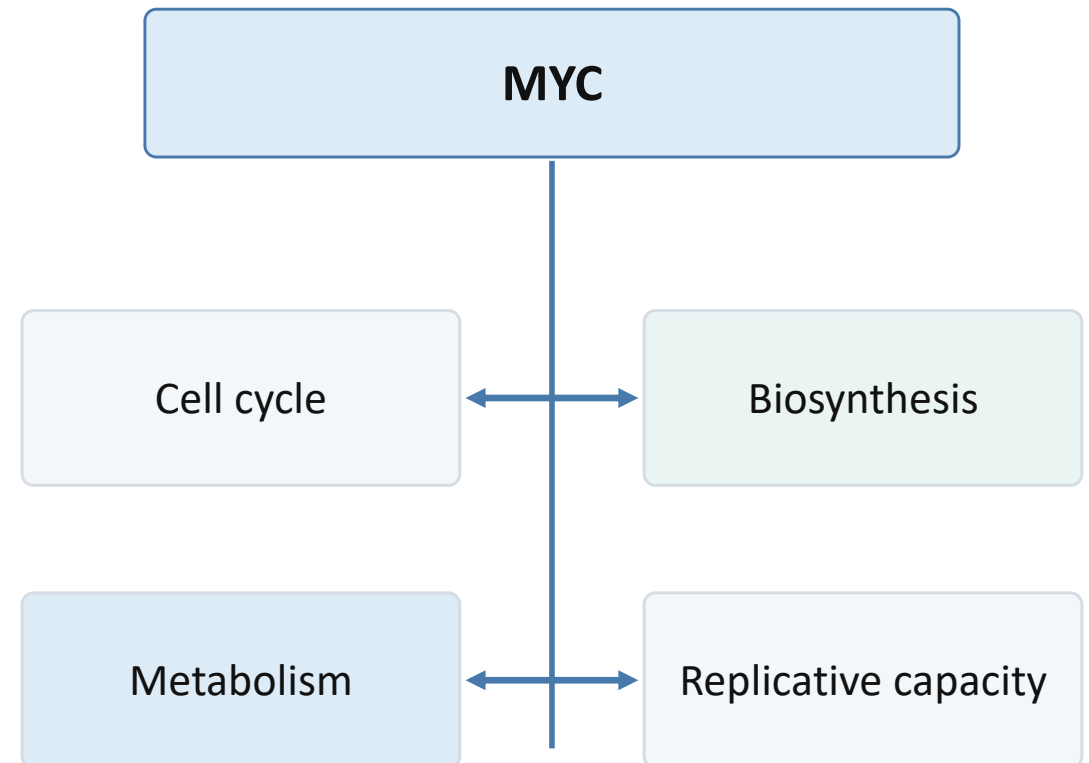
JUN

FOS

REL

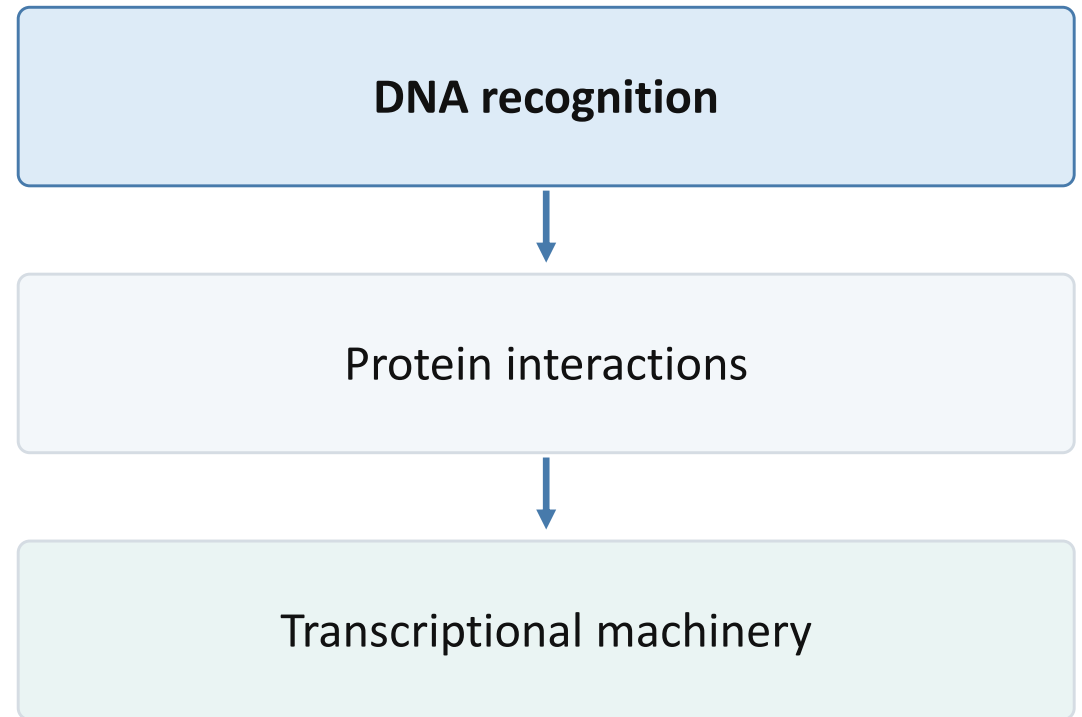
Why the lecture centers on MYC

- MYC is expressed in virtually all eukaryotic cells.
- Its abundance is rapidly modulated following mitogenic stimulation.
- Deregulated MYC is common across cancer types and alters multiple growth programs.



Transcription factors have modular functions

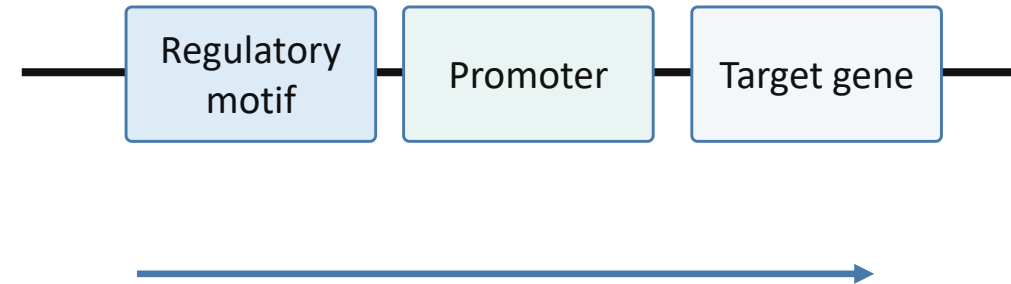
- DNA-binding regions recognize short regulatory sequences.
- Protein-interaction regions help recruit transcriptional machinery.
- Regulatory modifications can change localization, activity and turnover.



Specific DNA binding provides target selection

- Transcription factors bind regulatory DNA motifs rather than all genomic sequences.
- Motifs can lie near promoters or in distant enhancers.
- The combination of DNA sites and co-regulators determines transcriptional output.

Schematic: Regulatory DNA

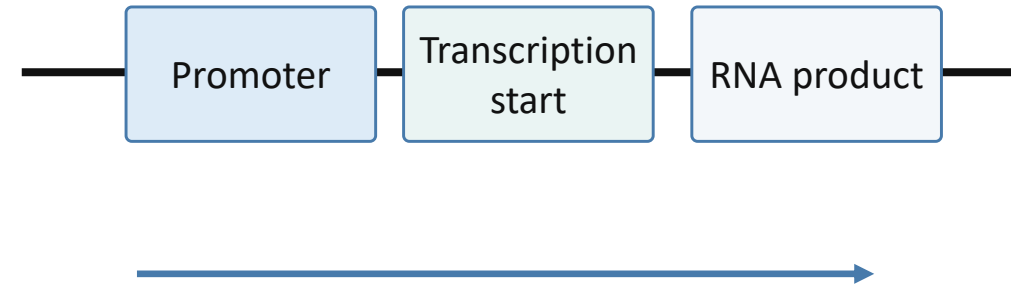


Regulatory relationships, not physical distances

Promoters and transcription initiation

- Promoters lie near the site where transcription begins.
- Bound factors and associated proteins help recruit RNA polymerase.
- Changes in promoter activity can increase target-gene RNA output.

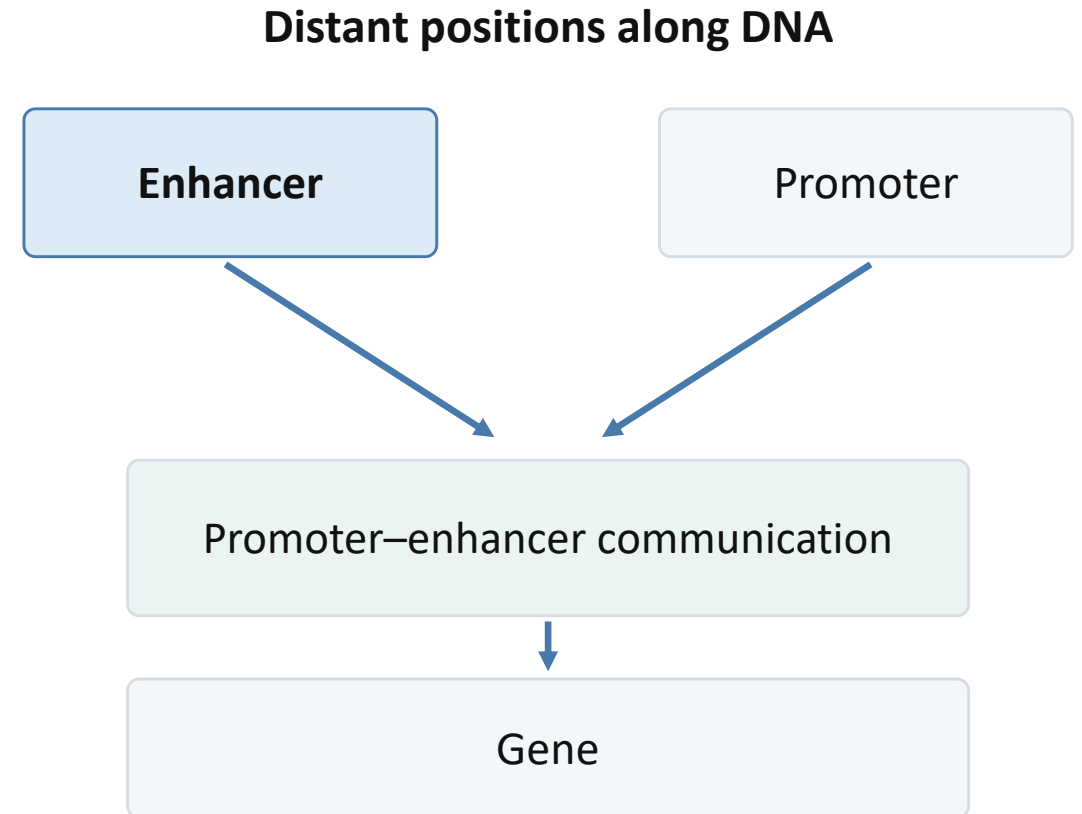
Schematic: Regulatory DNA



Regulatory relationships, not physical distances

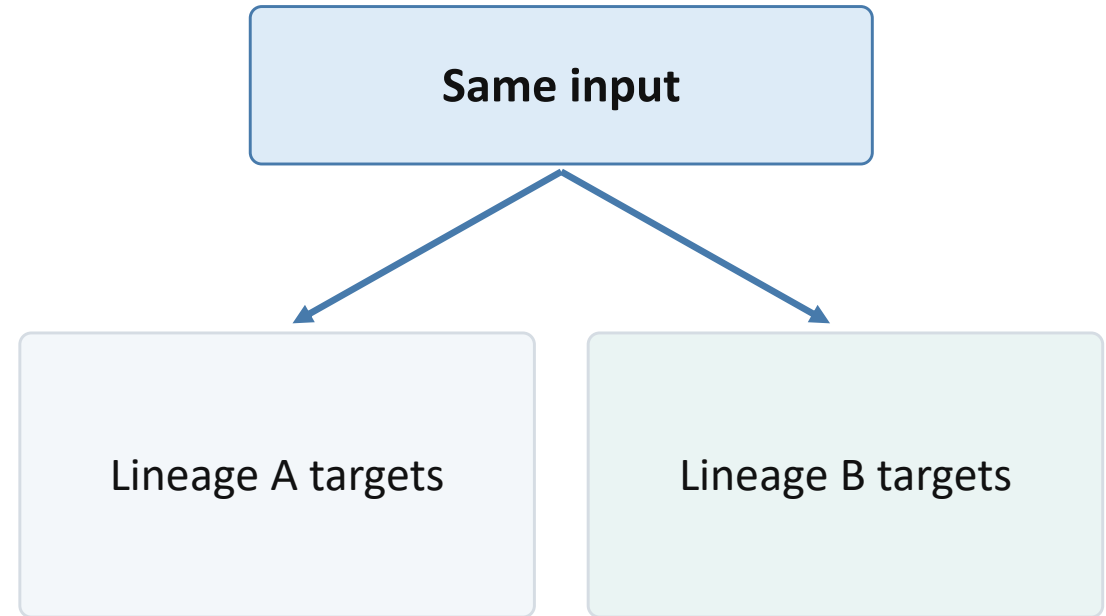
Enhancers regulate genes at a distance

- An enhancer can be far from its target promoter in the linear DNA sequence.
- Chromatin looping places enhancer-associated factors near promoter machinery.
- Enhancer activity can depend strongly on cell lineage.



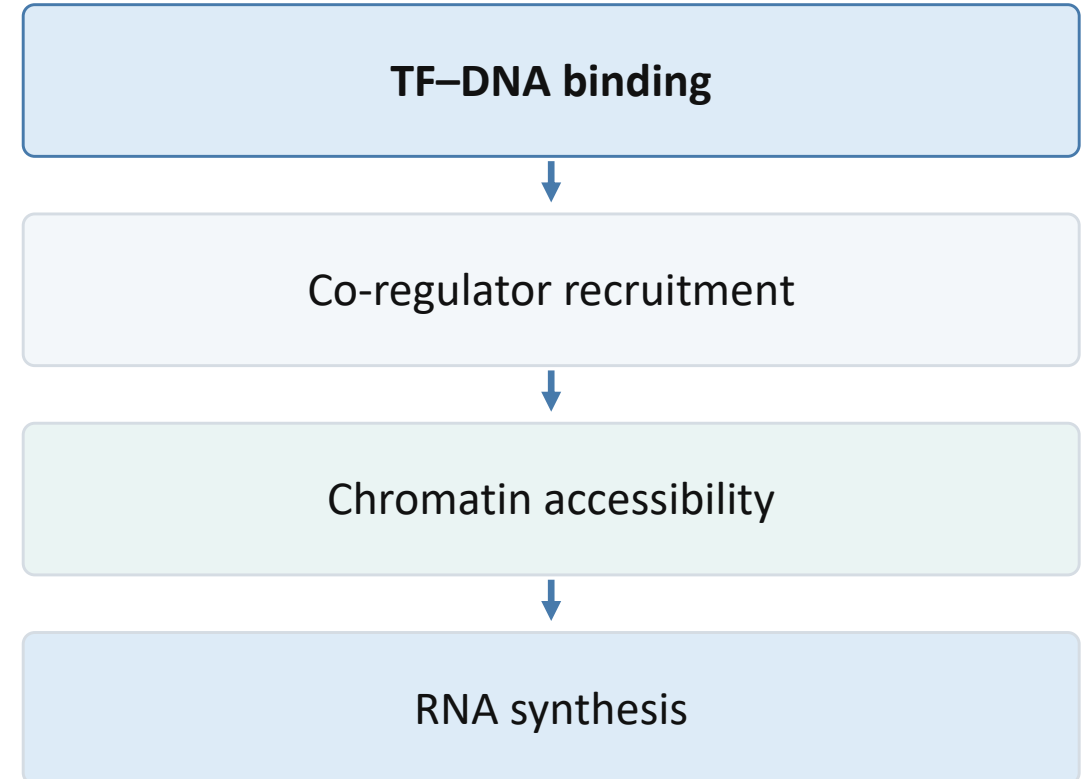
Chromatin context shapes the response

- A signal need not activate the same genes in every cell type.
- Lineage-specific enhancer contacts can change the transcriptional response.
- Therefore MYC activation mechanisms depend partly on cellular context.



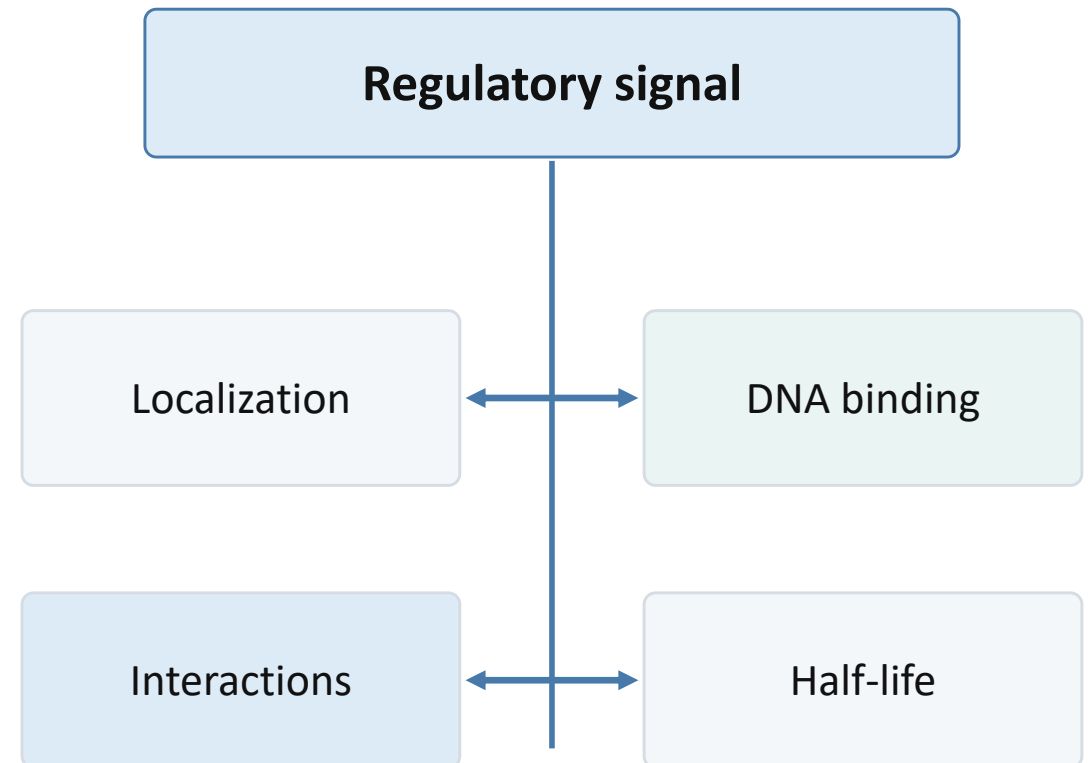
Co-regulators help transcription factors act

- Protein interactions recruit coactivators and chromatin-modifying proteins.
- Chromatin remodeling can expose transcription-initiation sites.
- RNA polymerase catalyzes synthesis of the resulting RNA.



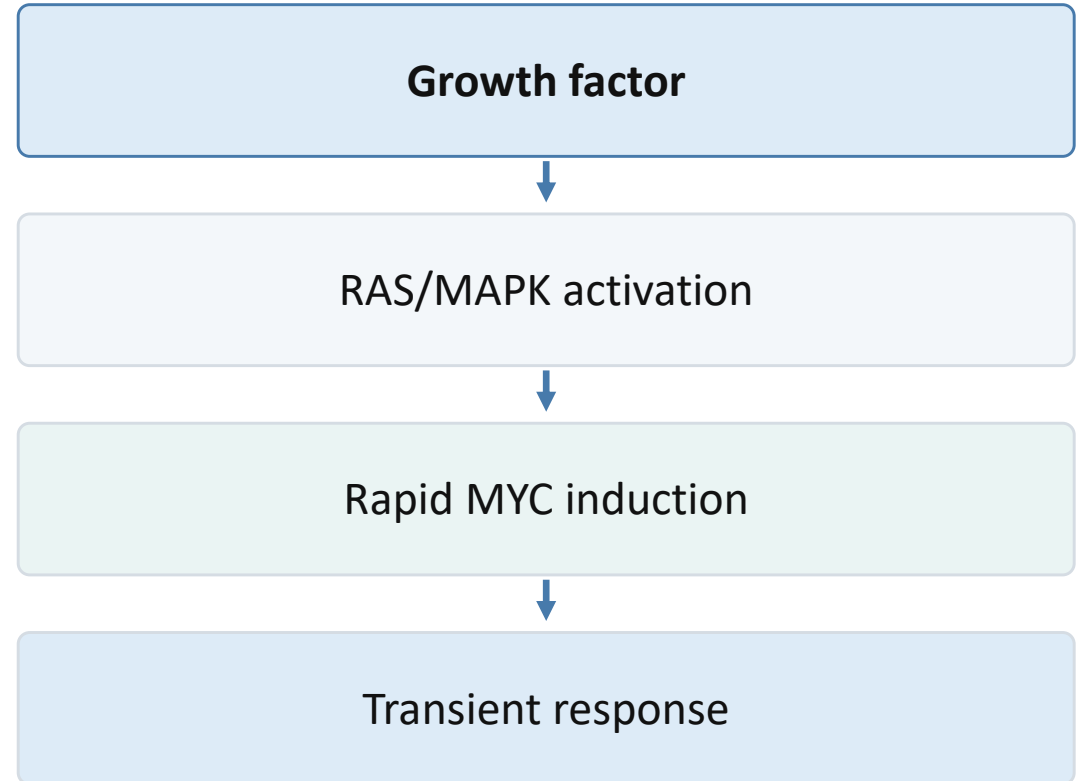
Signal-dependent transcription-factor control

- Posttranslational modifications can change nuclear localization.
- They may expose DNA-binding regions or promote protein interactions.
- They can also increase or decrease protein stability.



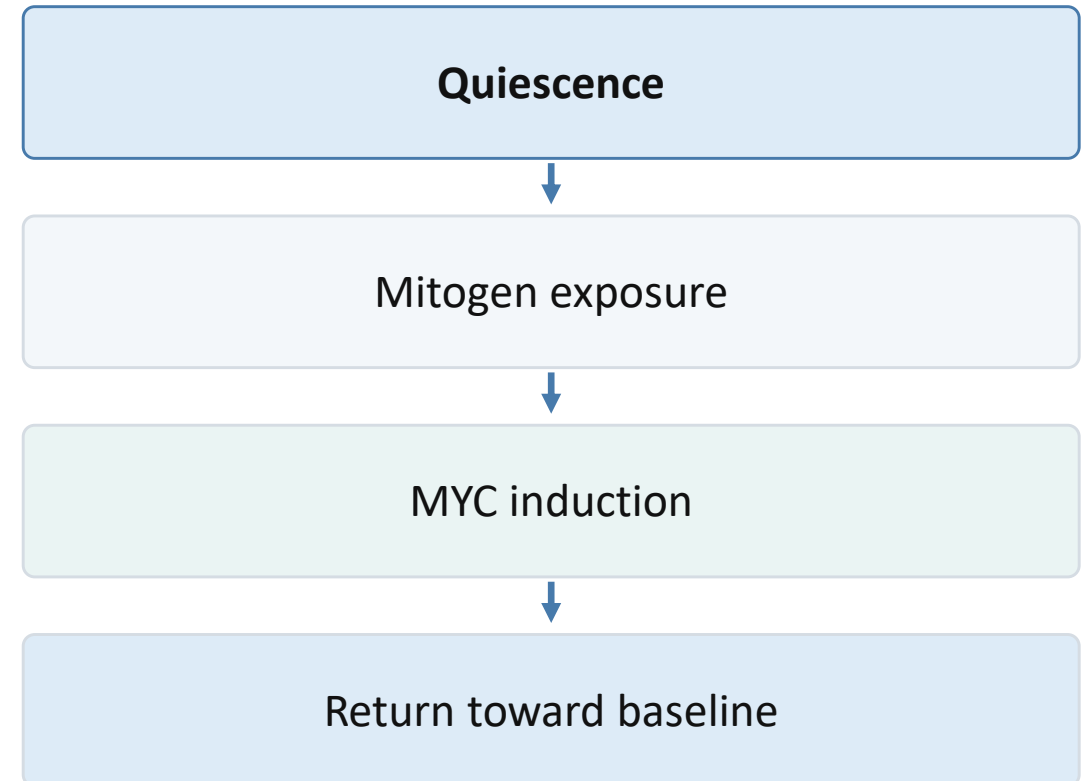
MYC is an immediate-early response gene

- Growth factor stimulation of quiescent cells activates RAS/MAPK signaling.
- MYC transcription responds rapidly to this input.
- The normal response is transient, not persistently maximal.



The normal MYC response is a controlled pulse

- Quiescent cells initially have low mitogen-induced MYC activity.
- Growth stimulation produces rapid MYC upregulation.
- Normal control limits the duration and abundance of MYC protein.



MYC abundance is regulated at three levels

- Transcription determines production of MYC RNA.
- Translation determines synthesis of MYC protein.
- Protein stability determines how long that protein remains available.

Distinct regulatory layers

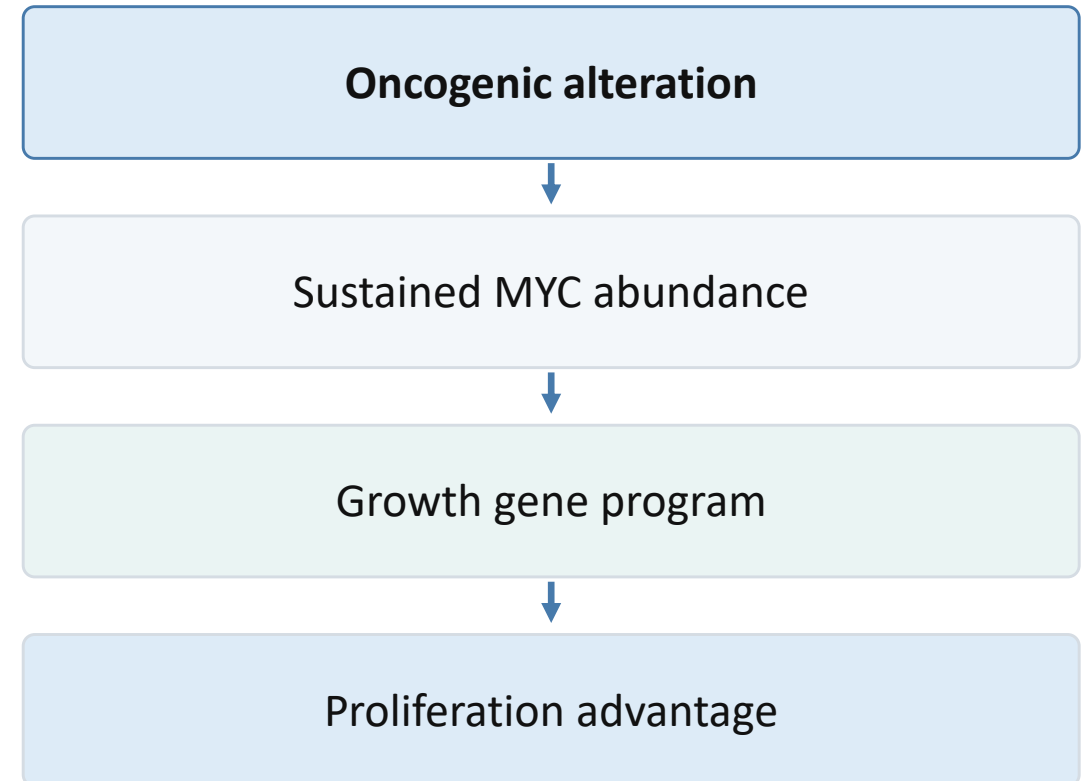
Transcription

Translation

Protein stability

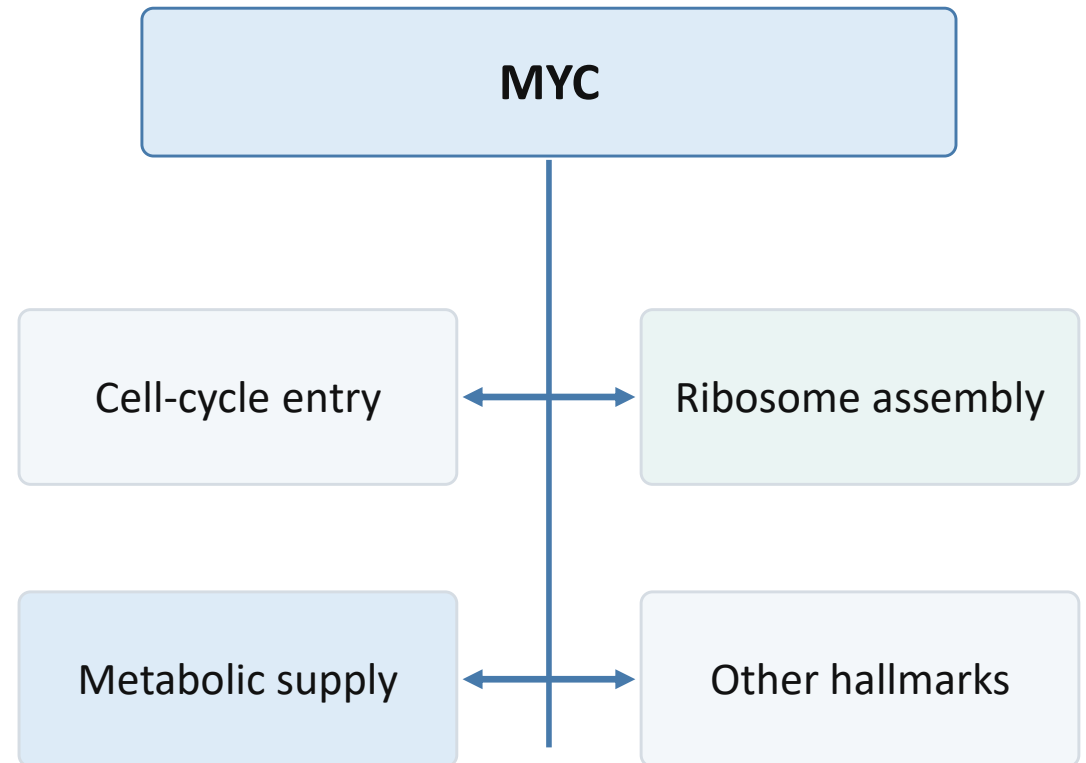
Cancer converts a transient program into persistence

- Inappropriate mitogenic signaling can maintain MYC activity.
- Direct oncogenic alterations may deregulate MYC independently.
- Persistent MYC can drive continuing expression of progrowth genes.



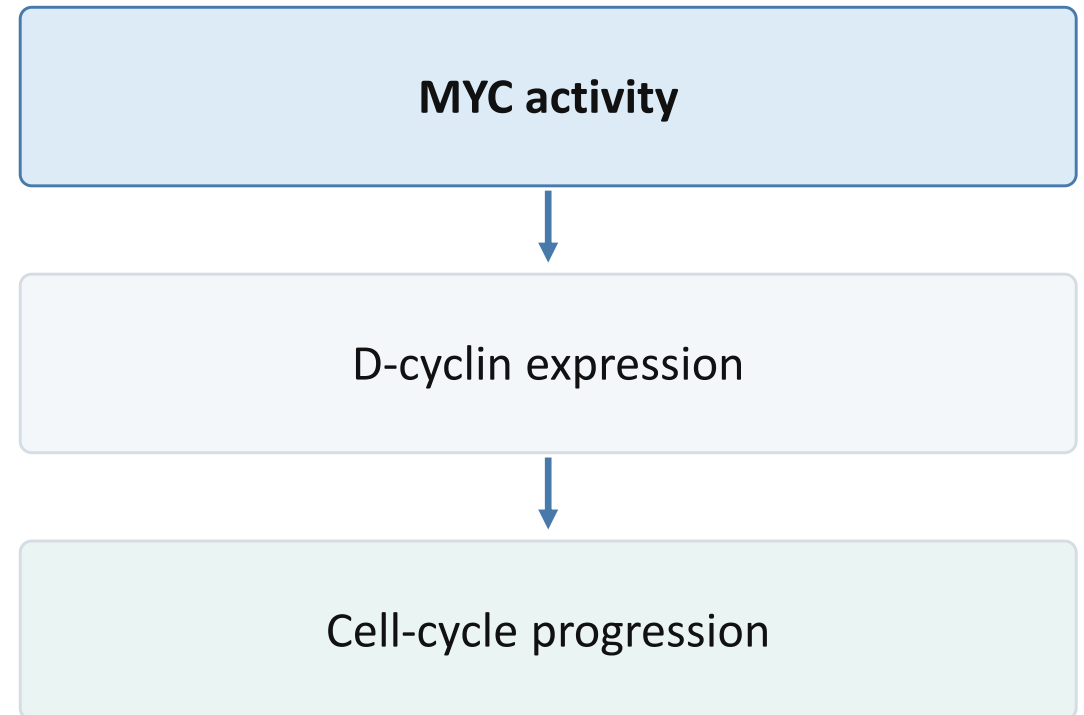
MYC has pleiotropic transcriptional effects

- MYC regulates gene expression programs with distinct cellular functions.
- Its consequences extend beyond cell-cycle entry.
- Many effects can cooperate within the same neoplastic cell.



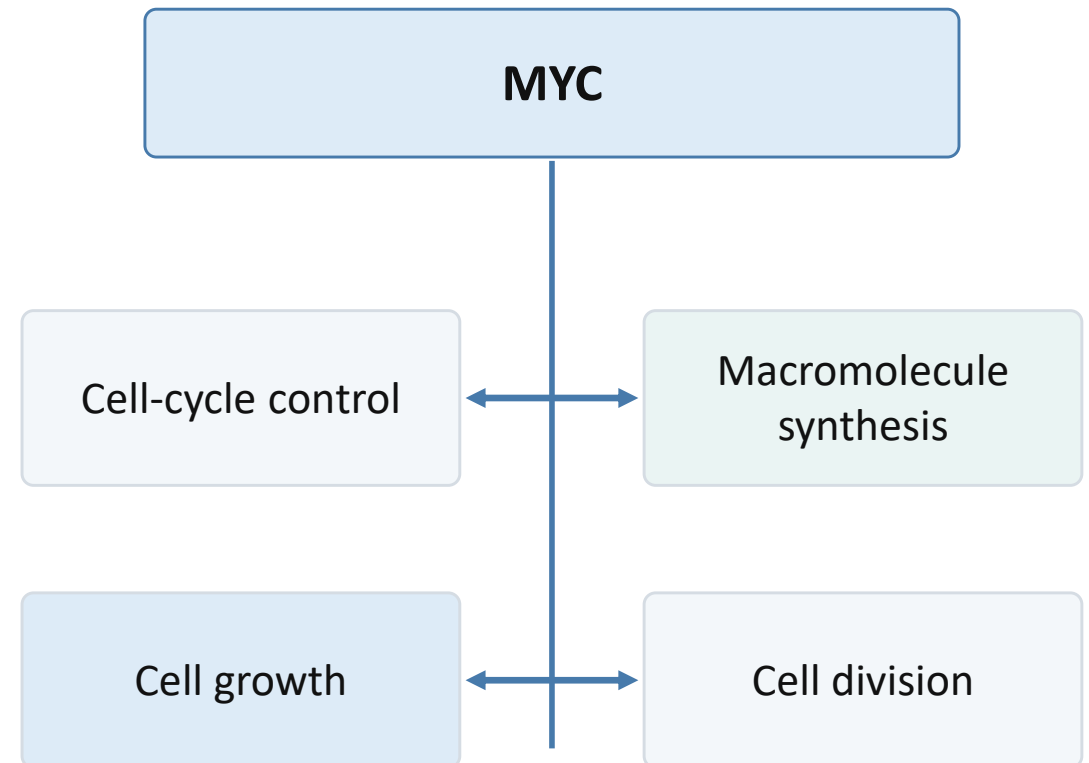
MYC promotes cell-cycle progression

- The MYC target-gene repertoire includes D cyclins.
- D cyclins participate directly in progression through the cell cycle.
- MYC therefore connects mitogenic signals with the cell-division machinery.



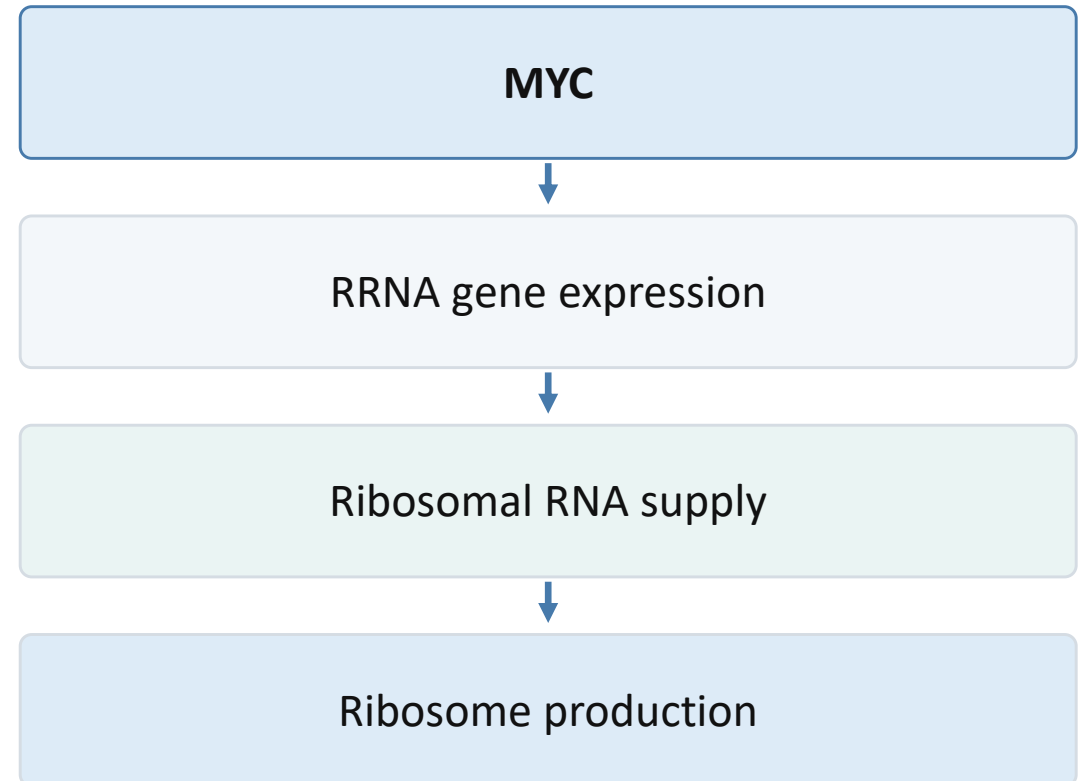
Division requires both regulatory and material inputs

- Cell-cycle regulation licenses progression through division.
- New cells also need proteins, lipids and nucleic acids.
- MYC contributes to both the regulatory and biosynthetic arms of growth.



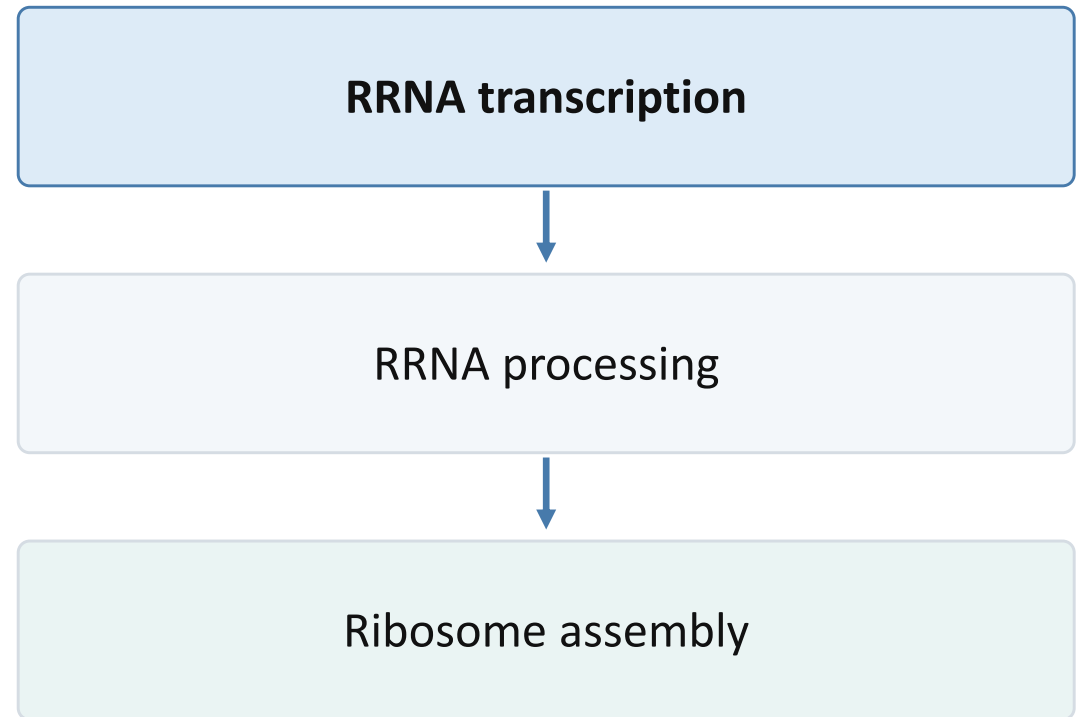
MYC increases ribosomal RNA production

- MYC upregulates transcription of ribosomal RNA genes.
- Ribosomal RNA is an essential structural and functional ribosome component.
- More rRNA supports the expansion of protein-synthesis capacity.



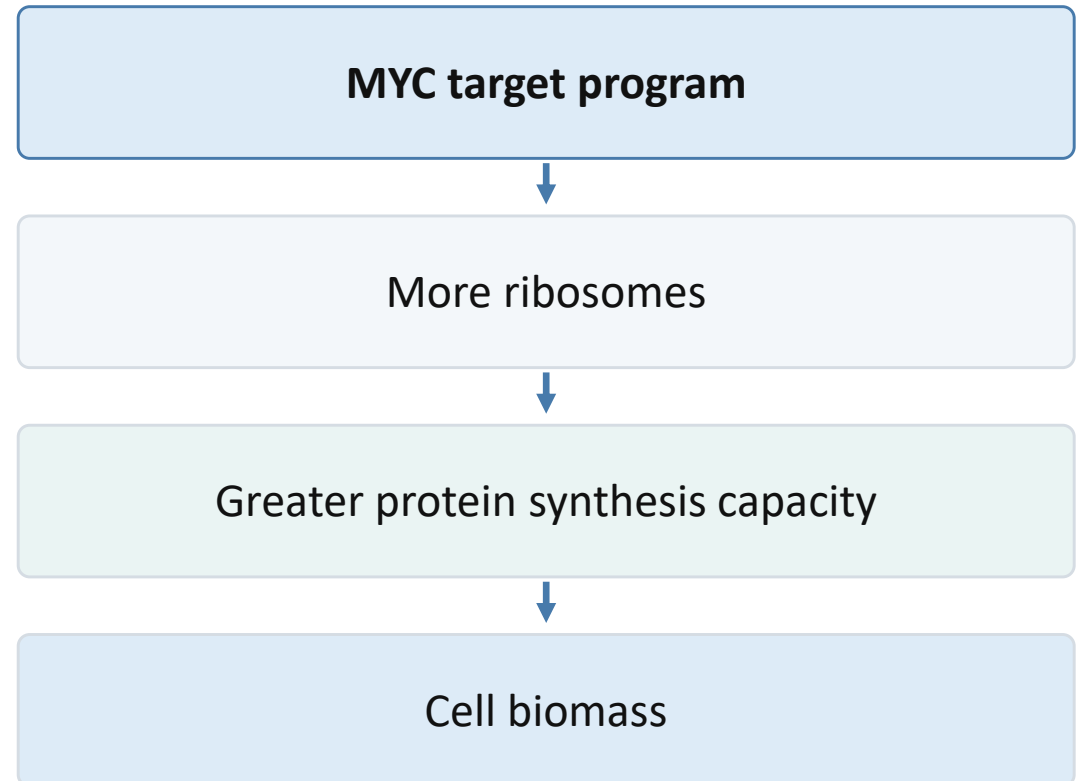
MYC also supports ribosomal RNA processing

- Newly transcribed rRNA must be processed before functional ribosomes assemble.
- MYC upregulates rRNA-processing processes as well as rRNA transcription.
- The combined effect facilitates ribosome assembly.



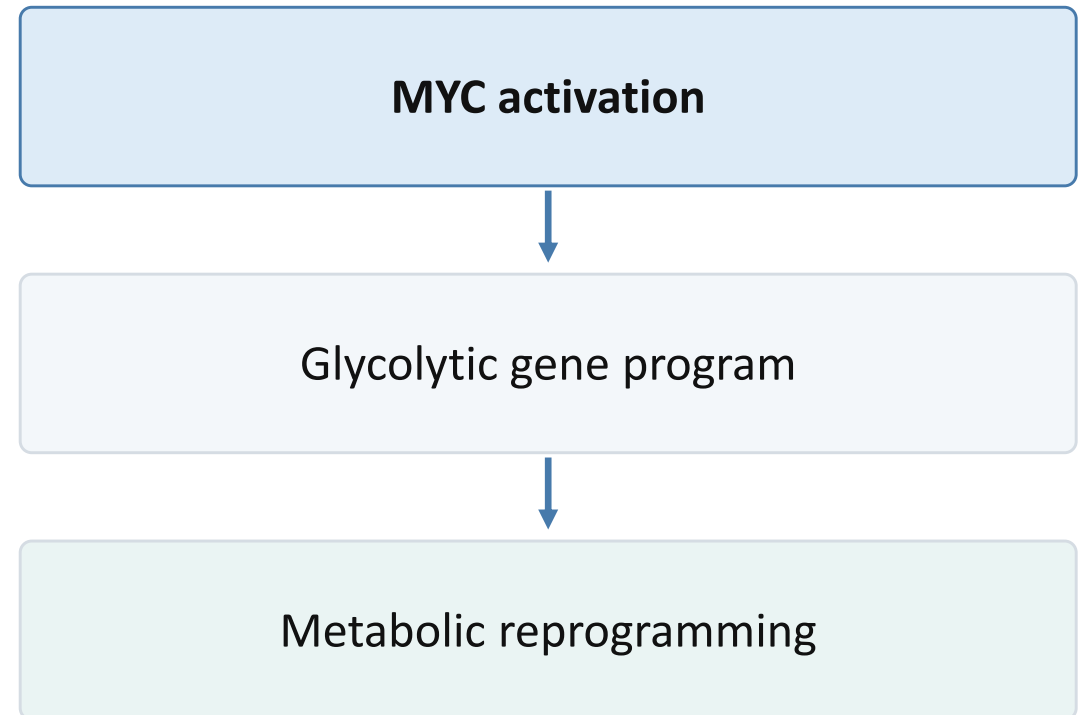
Ribosome biogenesis enables protein synthesis

- An expanding cell must synthesize structural and regulatory proteins.
- Ribosome assembly increases the capacity for translation.
- MYC-supported ribosome biogenesis links gene regulation to cell growth.



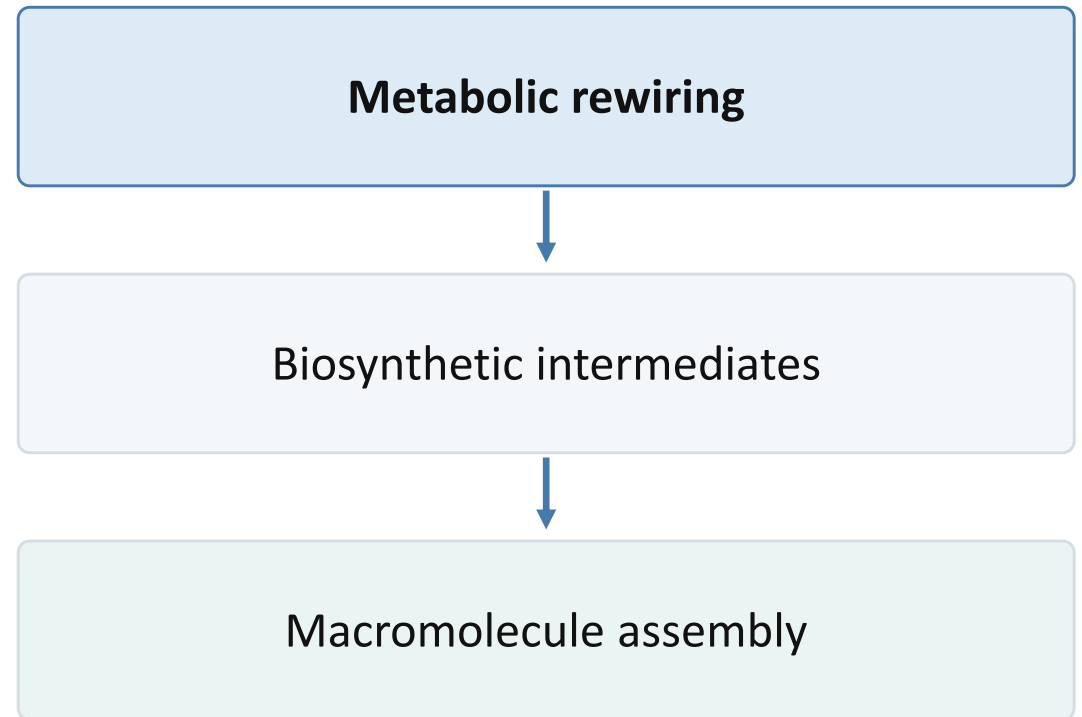
MYC upregulates glycolytic components

- MYC increases the expression of multiple glycolytic enzymes.
- This is part of a wider metabolic gene-expression program.
- The source associates this shift with the Warburg effect.



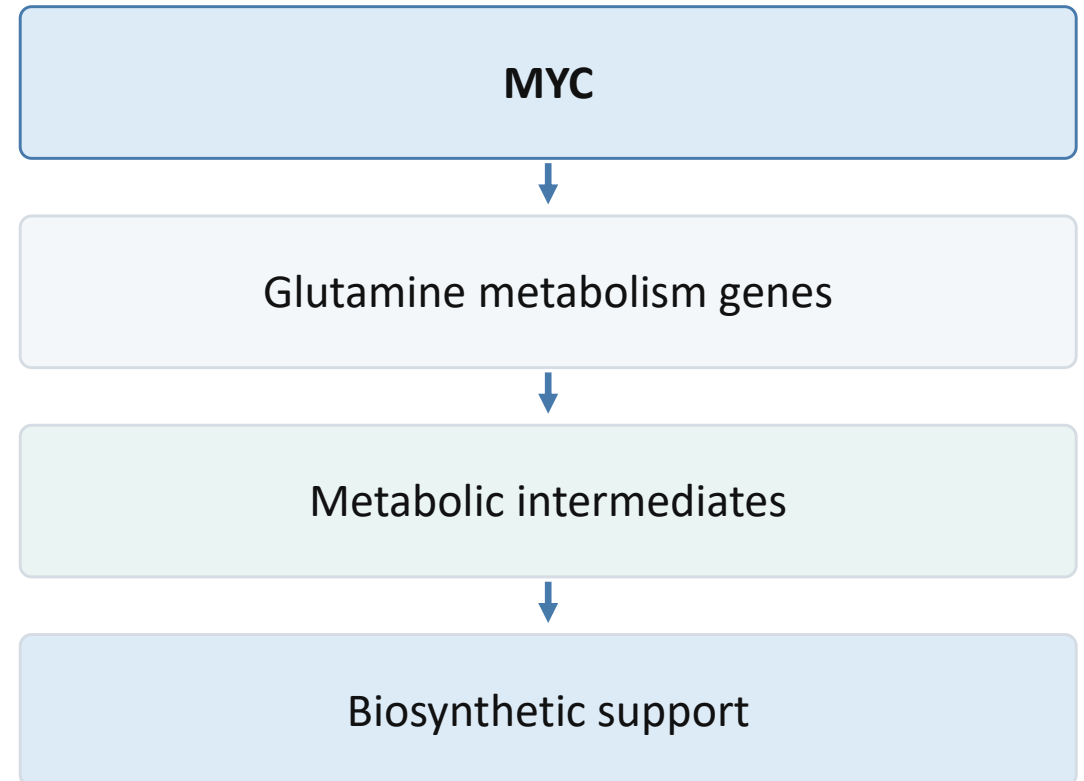
Metabolic reprogramming supports anabolic growth

- Altered carbon metabolism supplies intermediates for biosynthesis.
- The Warburg effect is discussed by Robbins as a cancer hallmark.
- The biological purpose is not limited to producing cellular energy.



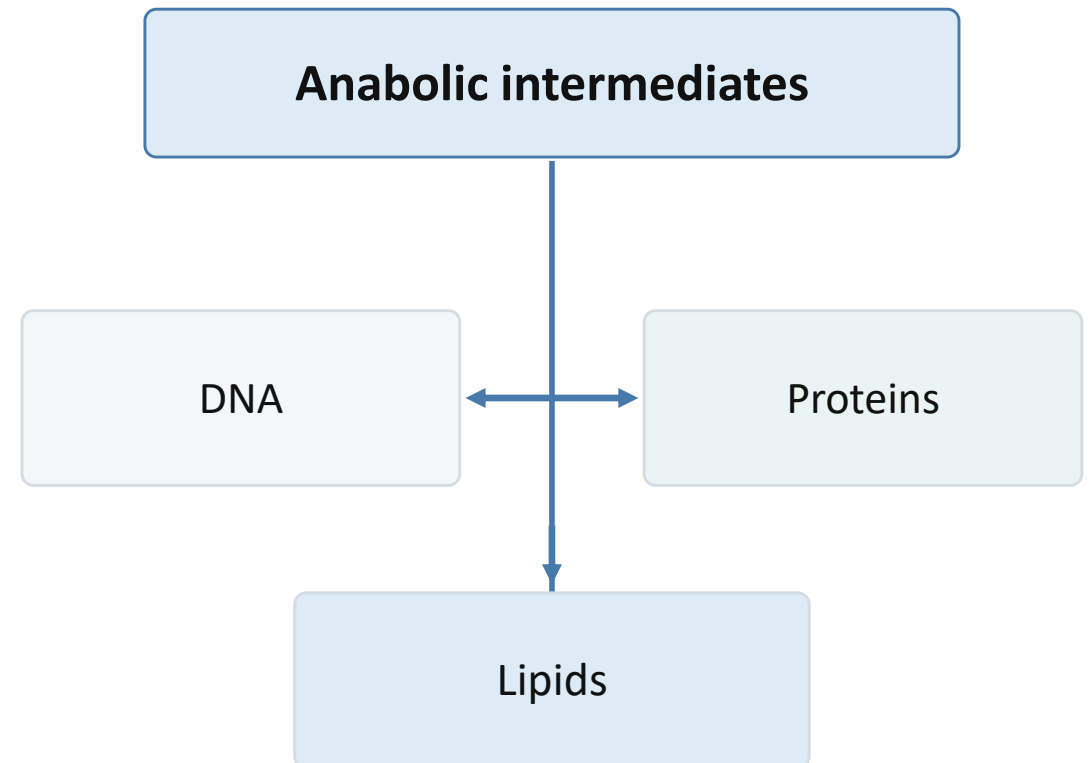
MYC also affects glutamine metabolism

- MYC regulates factors involved in glutamine utilization.
- Glutamine-related pathways contribute biosynthetic intermediates.
- This program cooperates with altered glycolysis to sustain growth.



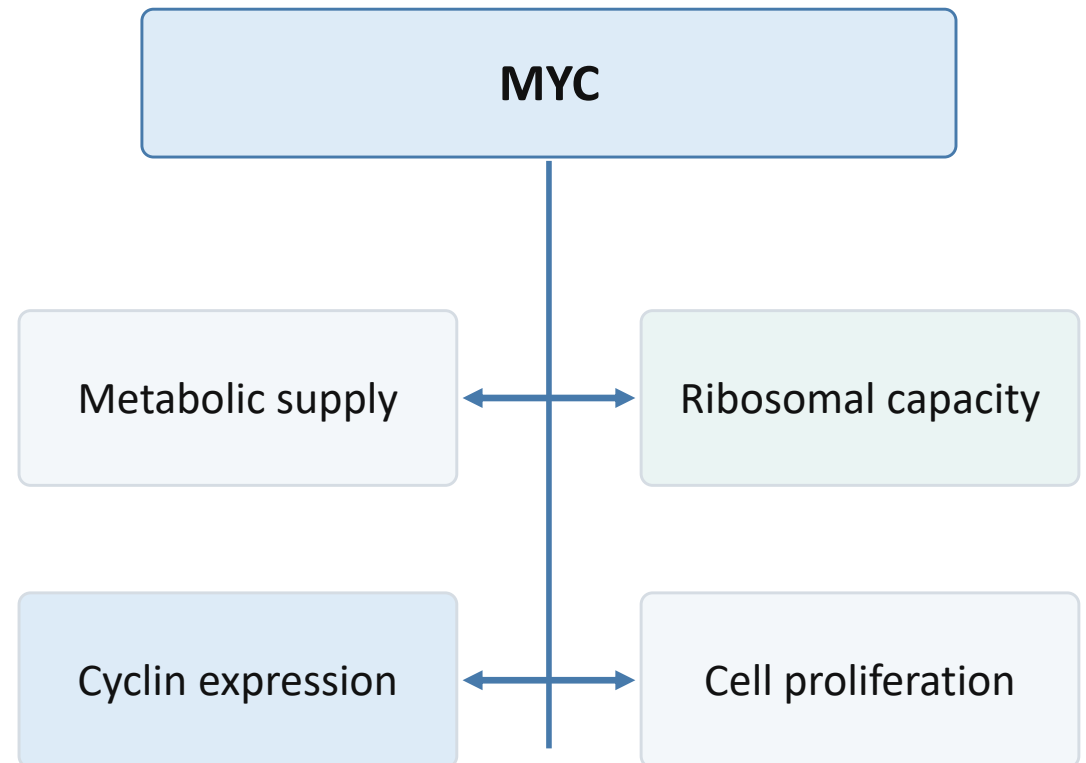
Building blocks are needed for daughter cells

- DNA synthesis requires nucleic-acid precursors.
- Proteins require amino acids and biosynthetic capacity.
- Cell membranes require lipid synthesis during growth.



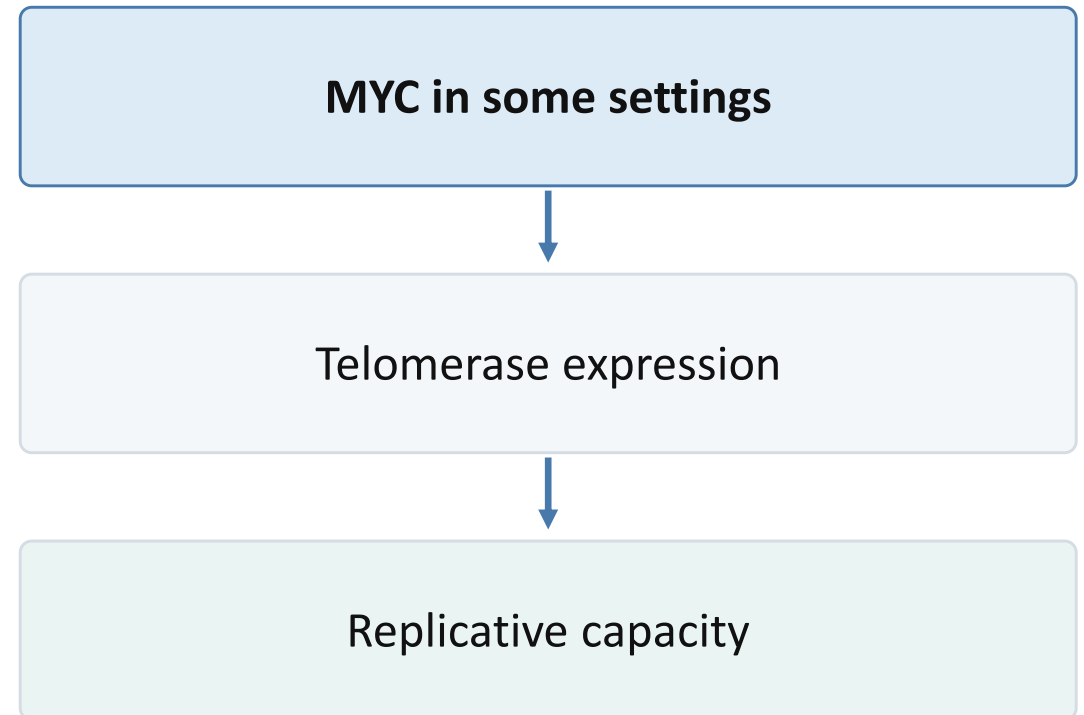
MYC coordinates metabolism and ribosome output

- Glycolysis and glutamine programs supply intermediates.
- Ribosome biogenesis provides capacity to translate proteins.
- Cell-cycle drivers determine whether division machinery proceeds.



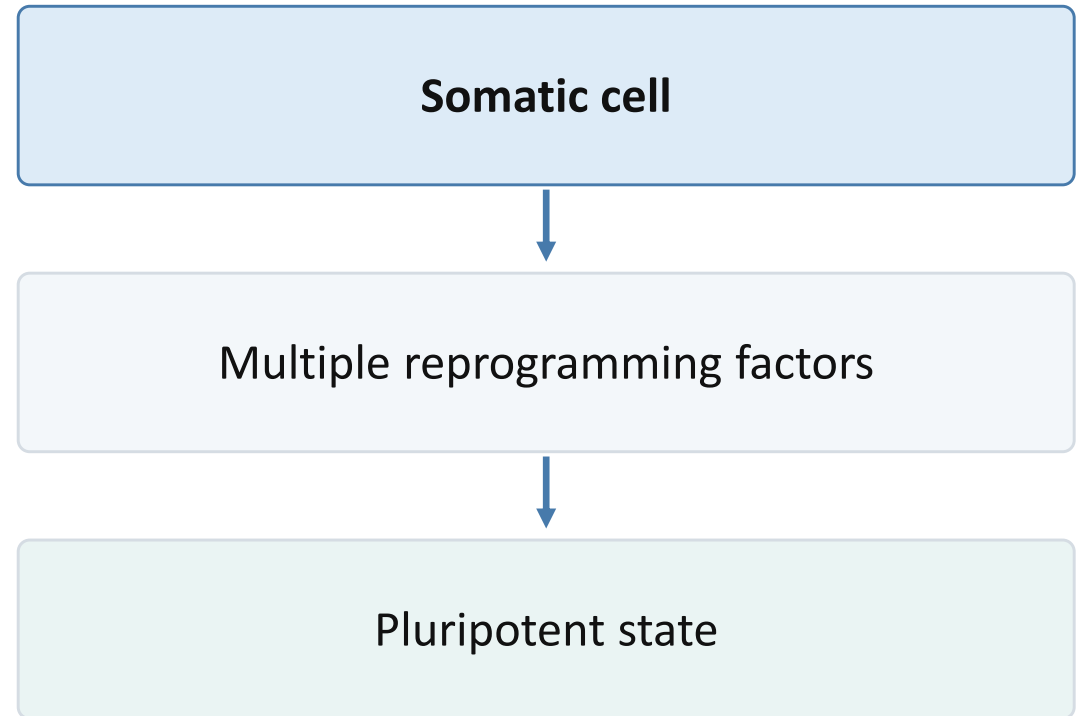
In some contexts, MYC increases telomerase

- The textbook specifically qualifies this effect as context-dependent.
- Telomerase is one contributor to replicative immortality.
- MYC regulation of telomerase is not presented as a universal cancer mechanism.



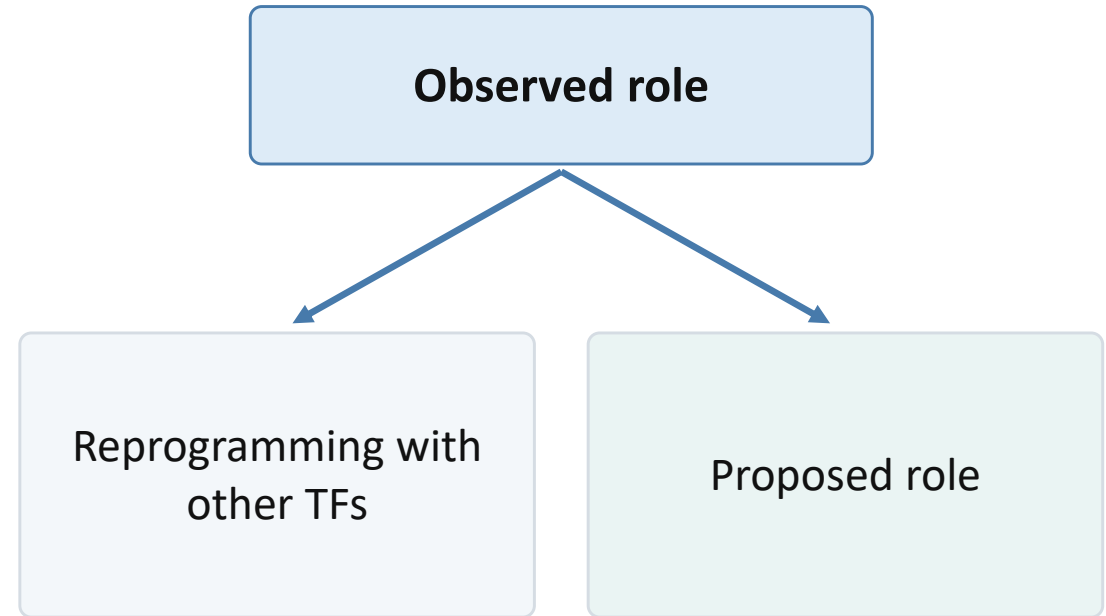
MYC participates in somatic-cell reprogramming

- MYC is among transcription factors that can act together in reprogramming.
- Reprogramming can produce pluripotent stem-cell states.
- The observation raises questions about similar programs in cancers.



MYC and cancer stemness: A hypothesis

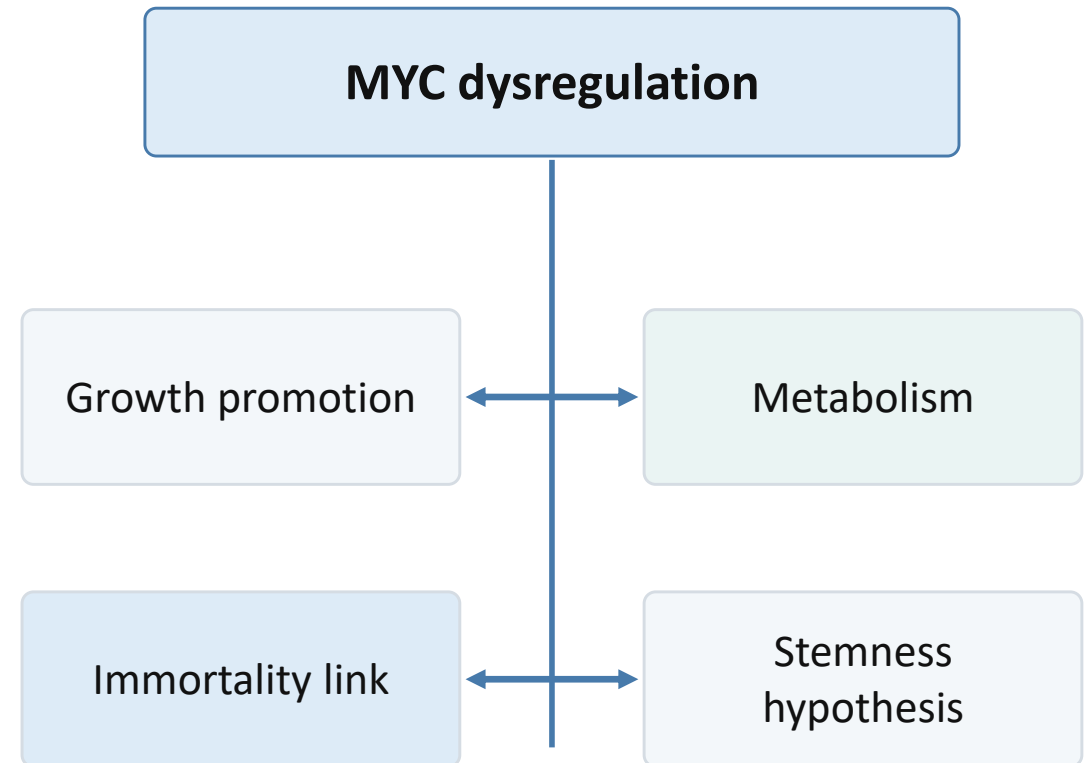
- A suspected contribution of MYC to cancer-cell stemness.
- This hypothesis follows from MYC participation in somatic-cell reprogramming.
- A possible relationship is not proof that all MYC-high tumors contain stemlike cells.



Cancer-cell stemness

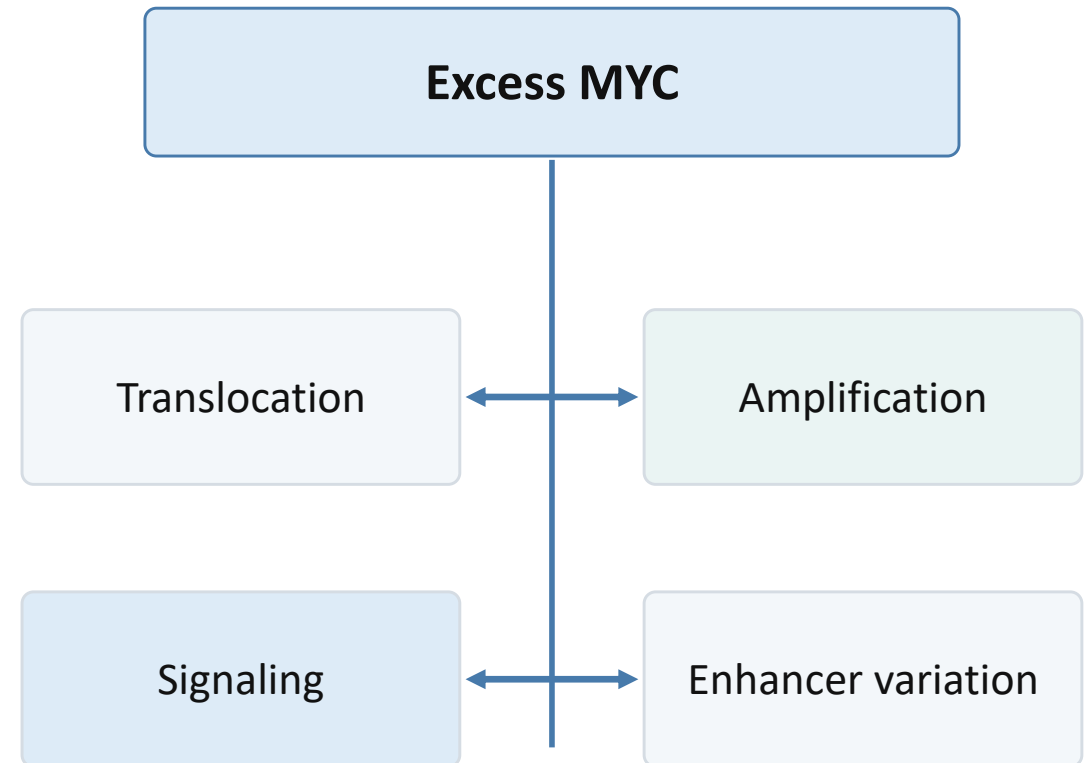
MYC links several cancer hallmarks

- Persistent expression promotes deregulated cell growth.
- Metabolic programs support the anabolic phenotype.
- Telomerase and reprogramming links suggest additional context-specific effects.



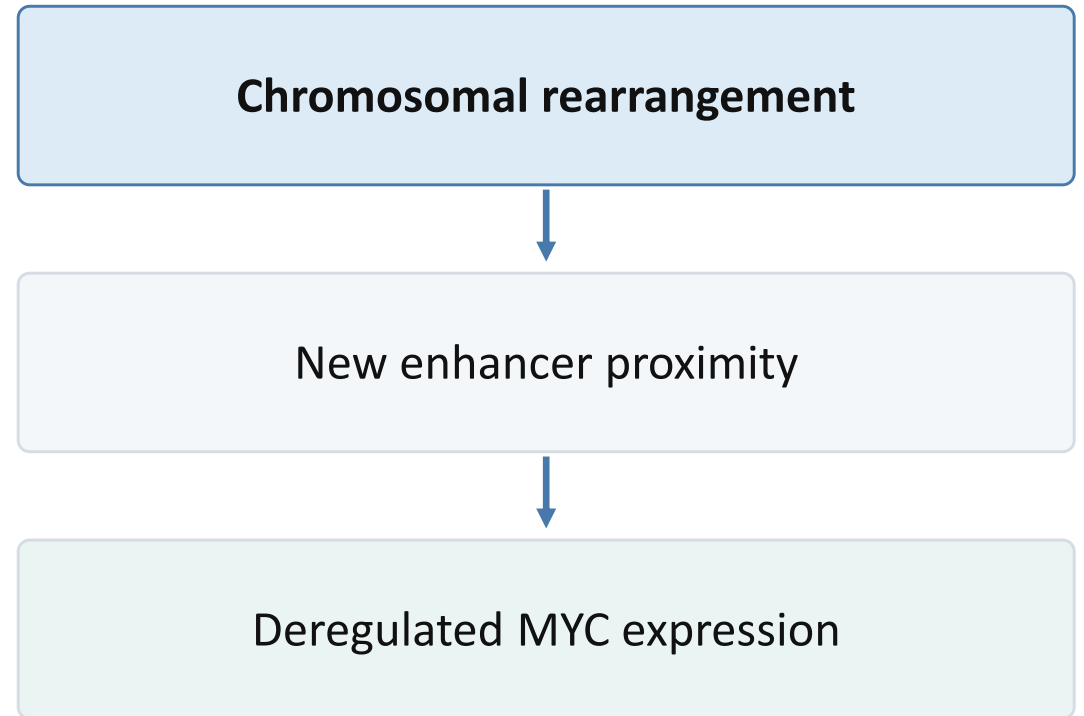
Four broad routes to increased MYC output

- Translocation can relocate MYC near a highly active enhancer.
- Amplification can increase copies of a MYC-family gene.
- Oncogenic upstream signaling can raise MYC protein levels.
- Inherited variants in nearby enhancers may alter responsiveness.



MYC translocation changes regulatory context

- A chromosomal rearrangement can reposition a normally regulated gene.
- The new locus can contain strong lineage-active enhancers.
- The rearranged gene is then abnormally expressed.



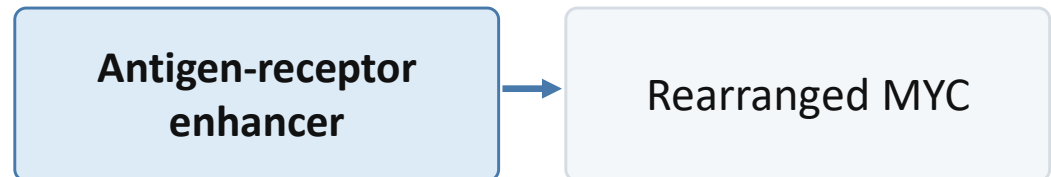
Antigen-receptor enhancers are highly active

- B- and T-lymphocyte receptor loci contain strong regulatory elements.
- In some lymphoid tumors, MYC moves into this enhancer-rich context.
- Antigen-receptor regulatory activity is redirected toward MYC.

Normal regulatory neighborhood



After regulatory juxtaposition

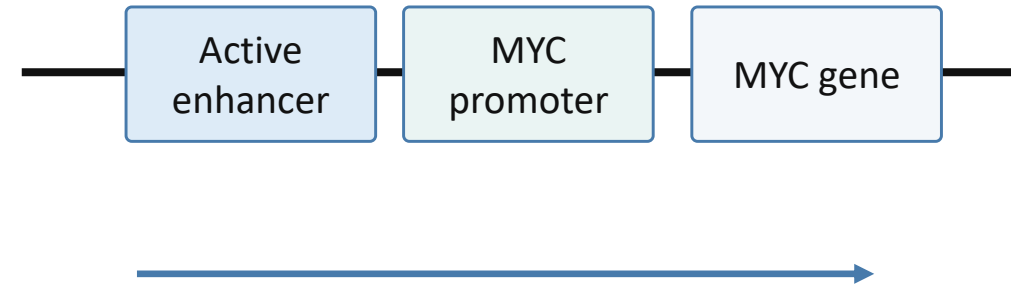


High MYC RNA

Enhancer hijacking is a cis-regulatory mechanism

- The active enhancer and MYC gene become juxtaposed by rearrangement.
- The enhancer stimulates excessive MYC transcription.
- Consequences follow from an altered DNA regulatory neighborhood.

Schematic: Regulatory DNA



Regulatory relationships, not physical distances

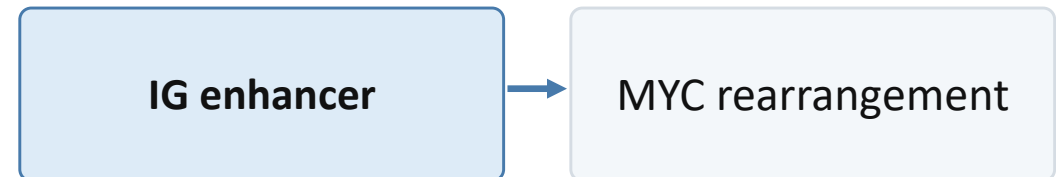
Burkitt lymphoma: Canonical MYC deregulation

- Burkitt lymphoma virtually always has a chromosomal translocation involving MYC.
- A common rearrangement juxtaposes MYC with an immunoglobulin locus.
- The associated enhancer drives unusually high MYC abundance.

Normal regulatory neighborhood



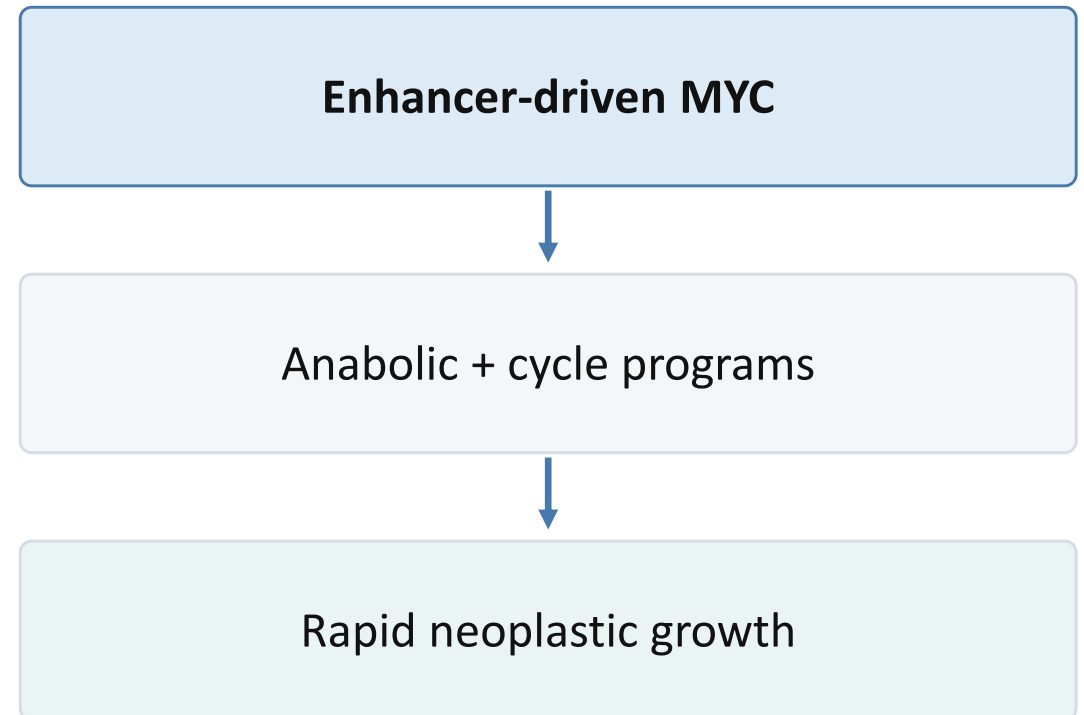
After regulatory juxtaposition



MYC overexpression

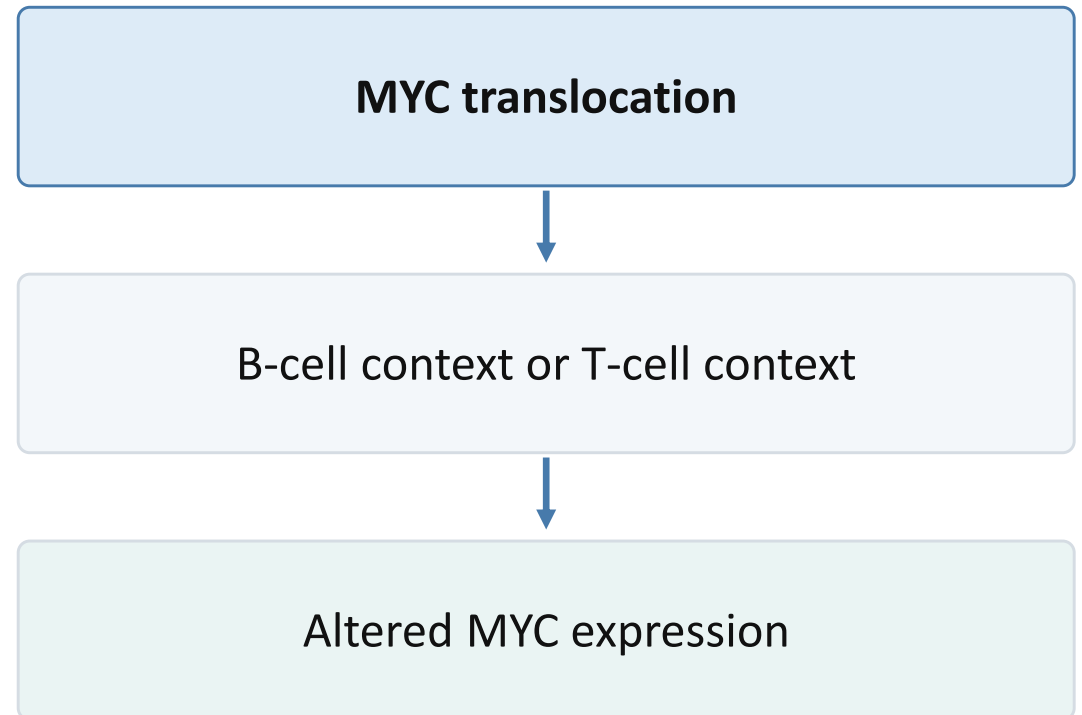
Why Burkitt lymphoma can grow so rapidly

- The source links very high MYC abundance with very fast tumor growth.
- The enlarged transcriptional program promotes biosynthesis and cell-cycle progression.
- This is a mechanistic explanation, not a quantified doubling-time estimate.



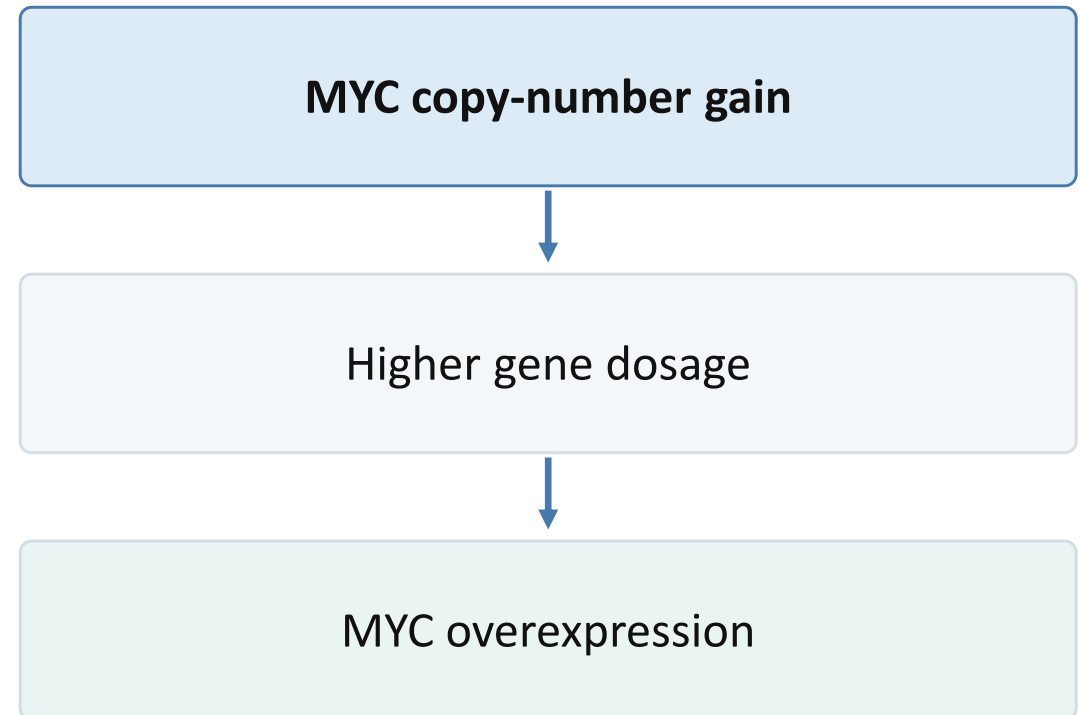
MYC translocations occur beyond Burkitt lymphoma

- The textbook mentions subsets of other B-cell neoplasms.
- It also describes MYC translocations in certain T-cell neoplasms.
- Molecular context must therefore be interpreted with the tumor phenotype.



Gene amplification is a second genetic route

- Amplification increases the number of gene copies in a neoplastic genome.
- Amplification of MYC can result in MYC overexpression.
- This differs mechanistically from enhancer relocation.



MYC amplification spans several solid tumors

- Robbins gives breast, colon and lung cancers as examples.
- Other tissues may also contain MYC-amplified tumors.
- These examples show that MYC deregulation is not confined to lymphoid tumors.

Breast

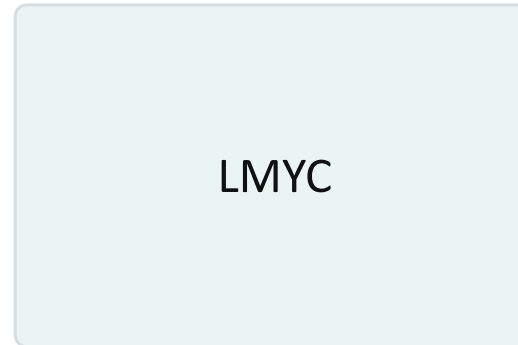
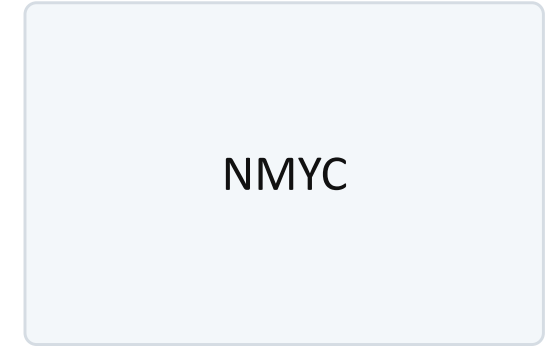
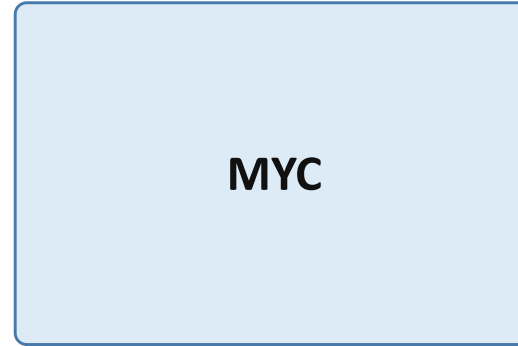
Colon

Lung

Other tissues

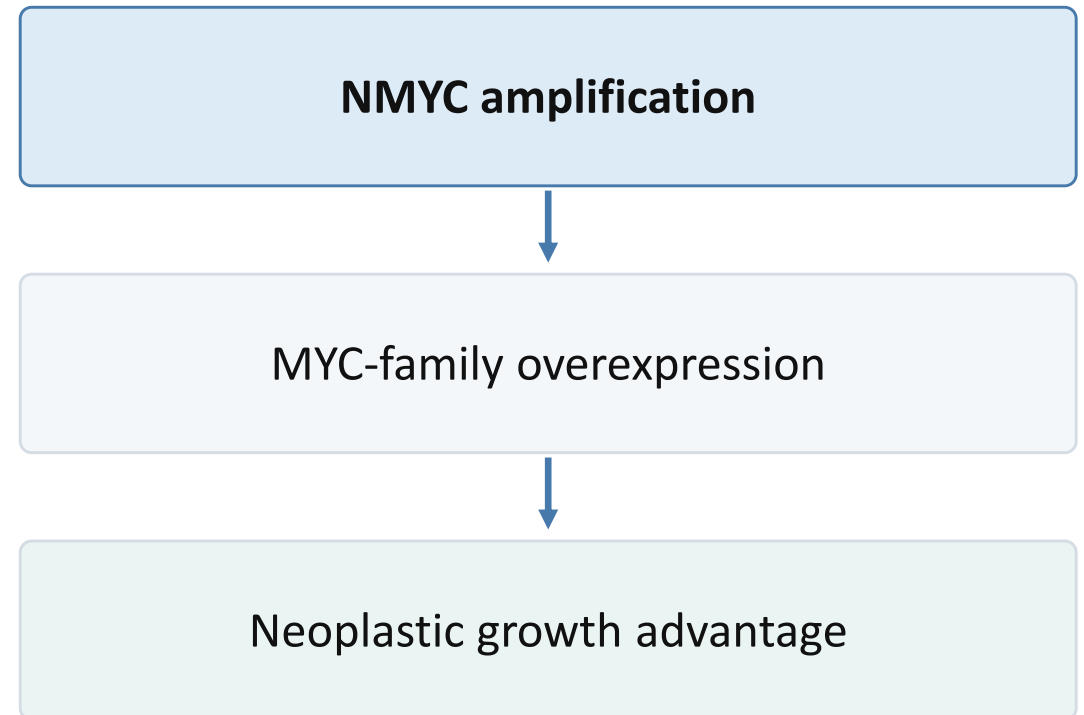
MYC-family paralogs extend the mechanism

- NMYC and LMYC as functionally identical related genes.
- Amplification can affect these MYC-family genes.
- Their cancer associations differ from MYC itself.



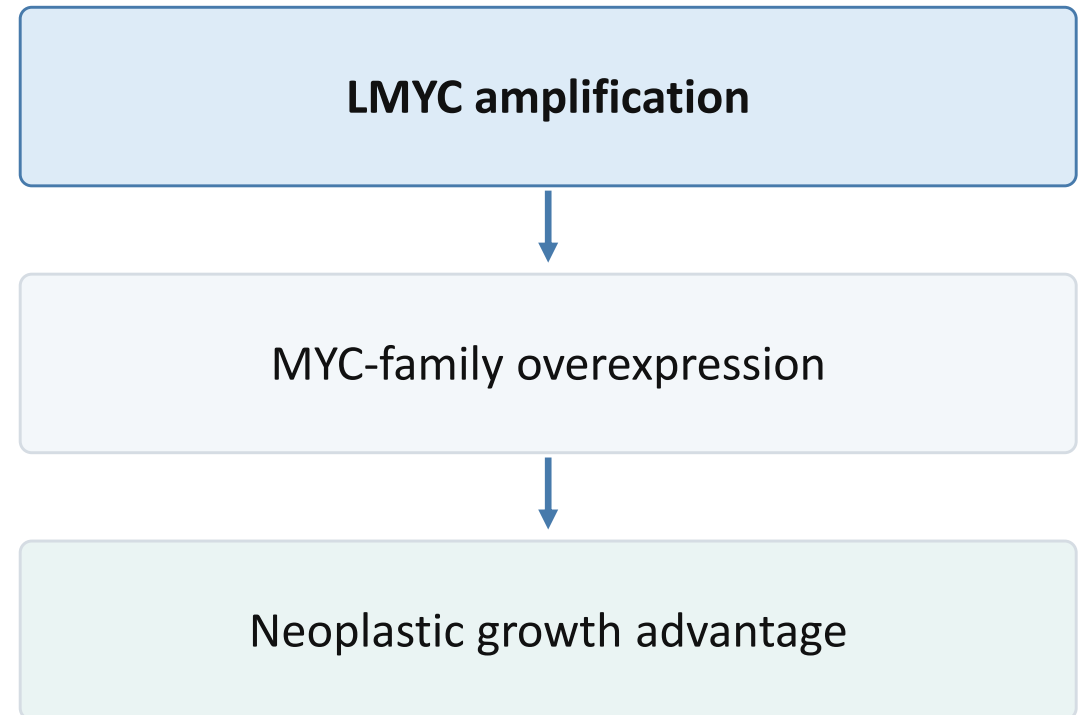
NMYC amplification in neuroblastoma

- Neuroblastoma is the canonical example given for NMYC amplification.
- The lesion increases a MYC-family growth-regulatory program.
- This example illustrates lineage-associated oncogene selection.



LMYC amplification in small-cell lung cancer

- LMYC amplification with small-cell lung cancers.
- The altered gene belongs to the same functionally related family.
- The mechanistic category is copy-number–driven transcription-factor activity.



Translocation and amplification are not synonyms

Translocation

Rearranges chromosomal position.

Can place MYC beside a strong enhancer.

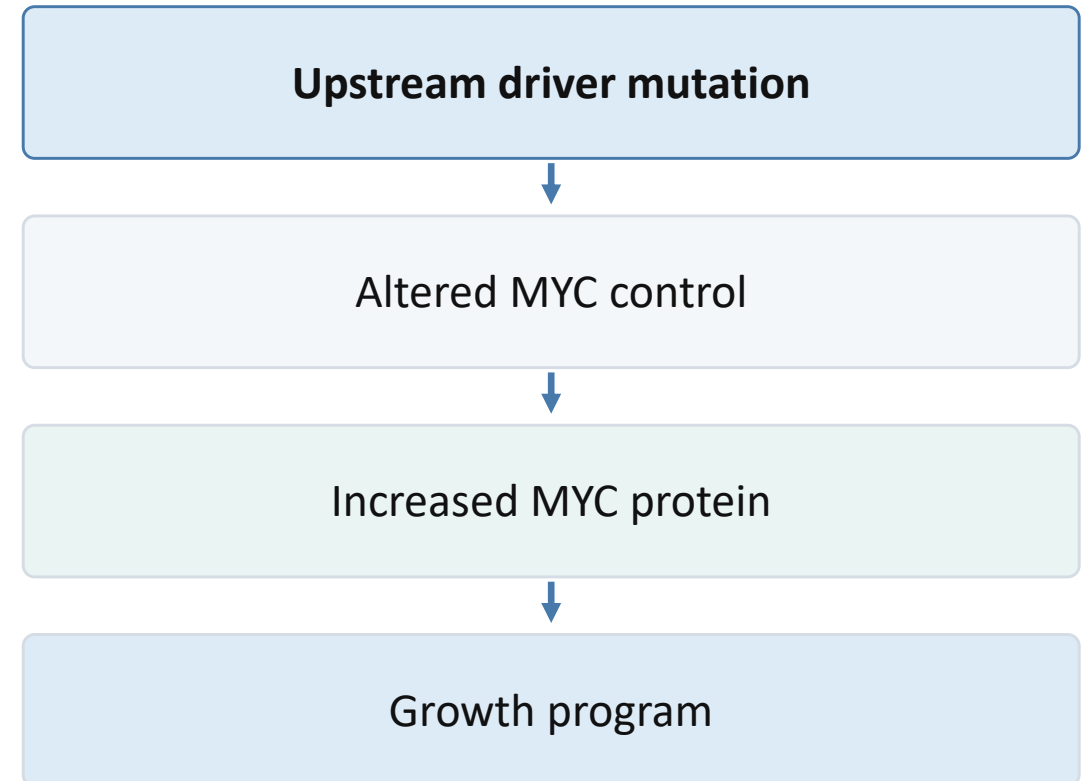
Amplification

Increases gene copy number.

Can elevate expression via increased dosage.

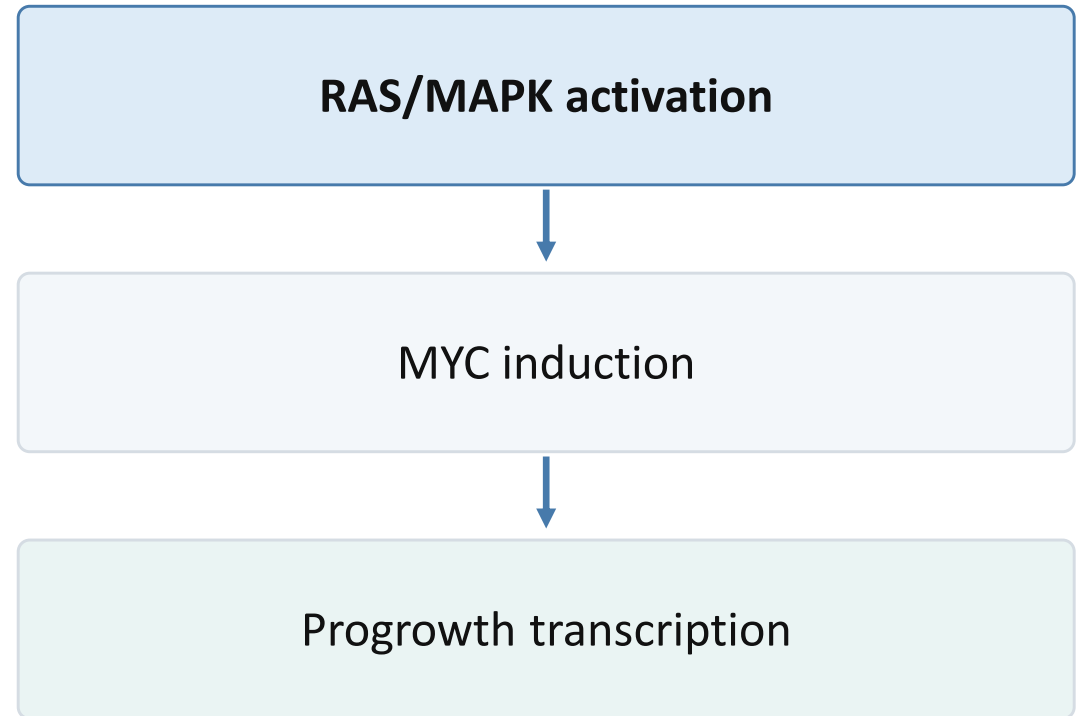
MYC elevation need not involve MYC DNA itself

- Cancer-associated pathway alterations can increase MYC transcription.
- They can also enhance translation or prolong protein stability.
- The result is excessive MYC even without a direct MYC rearrangement.



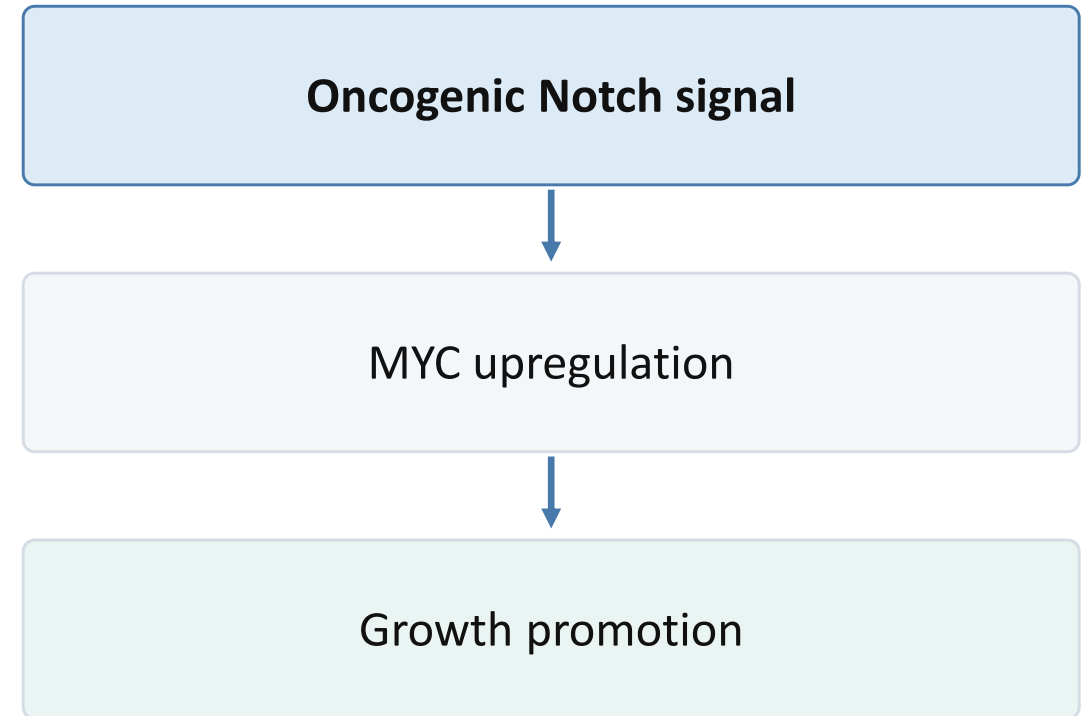
RAS/MAPK signaling raises MYC expression

- Physiologic RAS/MAPK activity can transiently induce MYC.
- Constitutive pathway signaling can maintain MYC abundance.
- The source notes this relationship in many different cancers.



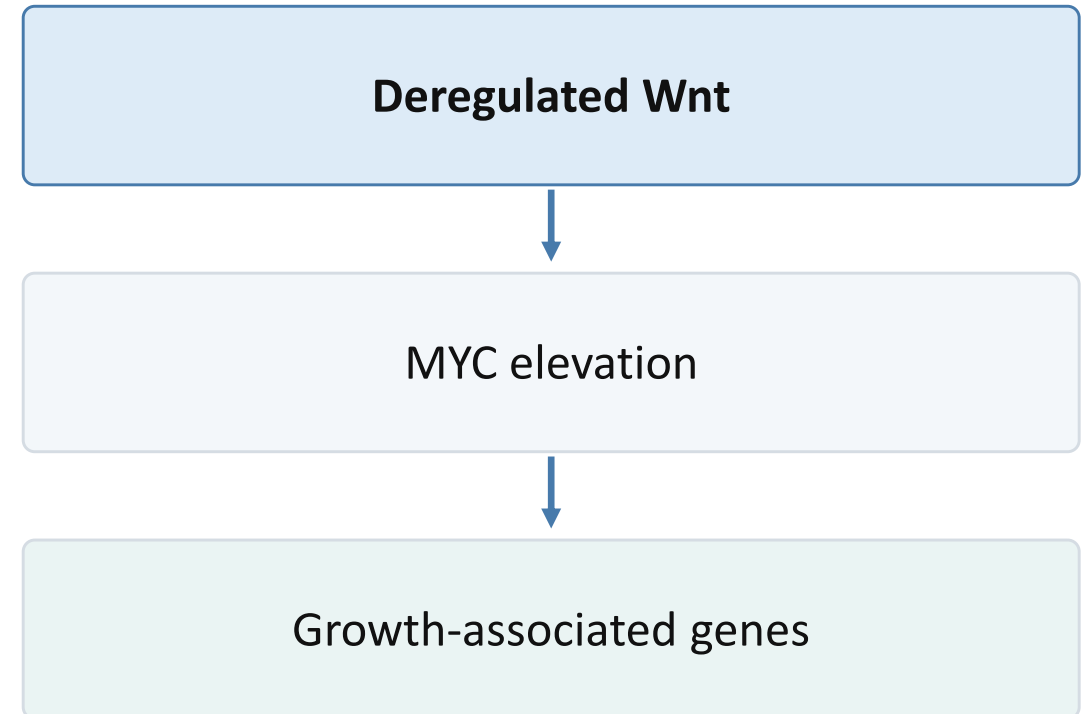
Notch signaling can converge on MYC

- Aberrant Notch signaling is another cited route to MYC activation.
- Robbins gives several cancers as the clinical setting.
- The transcriptional consequences vary with cellular context.



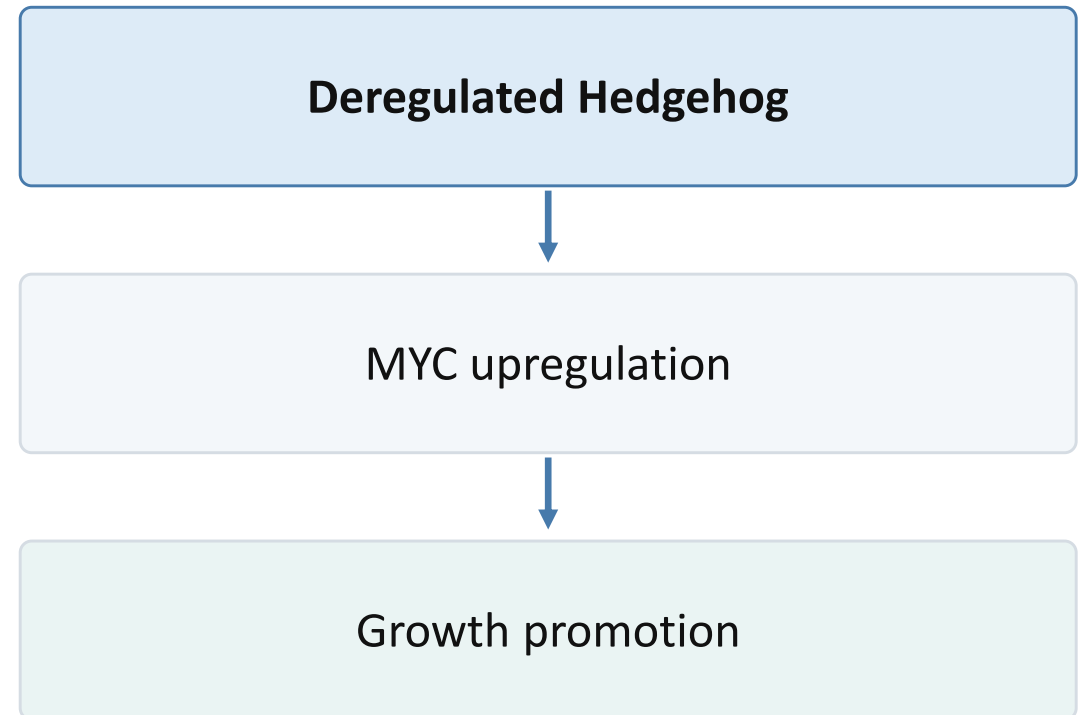
Wnt signaling provides a colon-cancer example

- The source lists Wnt-pathway activation in colon carcinoma.
- One consequence is MYC upregulation.
- MYC is an output effector, not necessarily the initiating pathway lesion.



Hedgehog signaling links to MYC in medulloblastoma

- Hedgehog-pathway dysregulation is listed in medulloblastoma.
- This pathway can promote transformation partly through MYC upregulation.
- The importance of this route depends on tumor context.



Pathways converging on MYC

Upstream pathway	Cancer context	Shared downstream theme
RAS/MAPK	Many cancers	Increased MYC abundance
Notch	Several cancers	MYC upregulation
Wnt	Colon carcinoma	MYC upregulation
Hedgehog	Medulloblastoma	MYC upregulation

MYC overexpression can arise at different stages

- Increased transcription generates more MYC RNA.
- Enhanced translation yields more MYC protein from available RNA.
- Protein stabilization extends the time MYC remains available.

Distinct regulatory layers

More MYC transcription

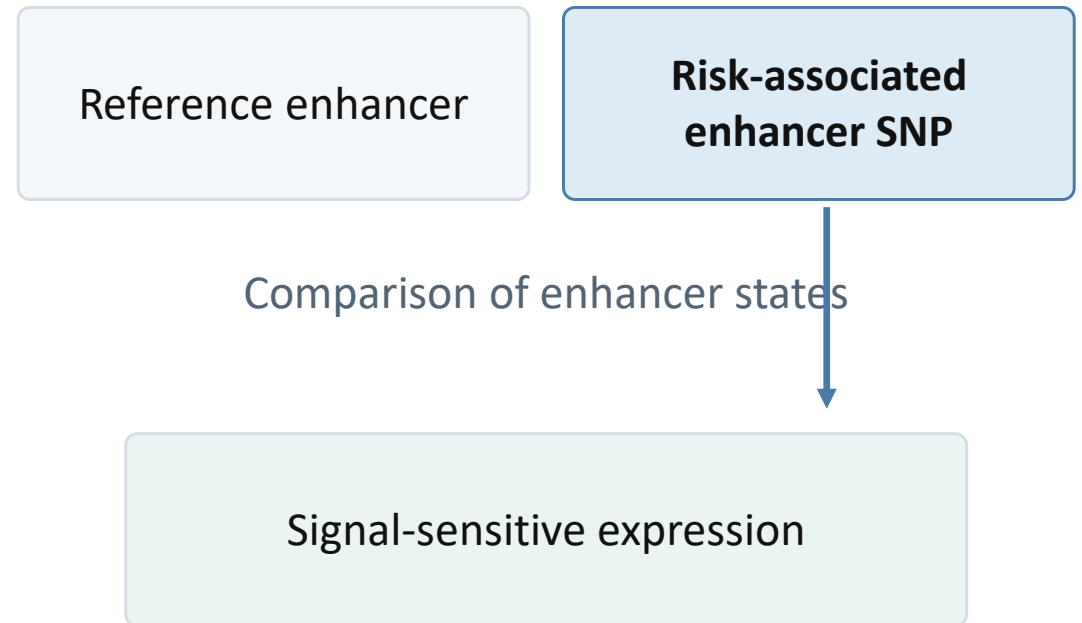
Greater MYC translation

Reduced protein turnover

Noncoding variants can affect MYC regulation

- Cancer-risk–associated SNPs may lie in enhancers near MYC.
- Such variants can increase responsiveness to growth-promoting signals.
- Regulatory DNA can therefore influence cancer susceptibility without coding change.

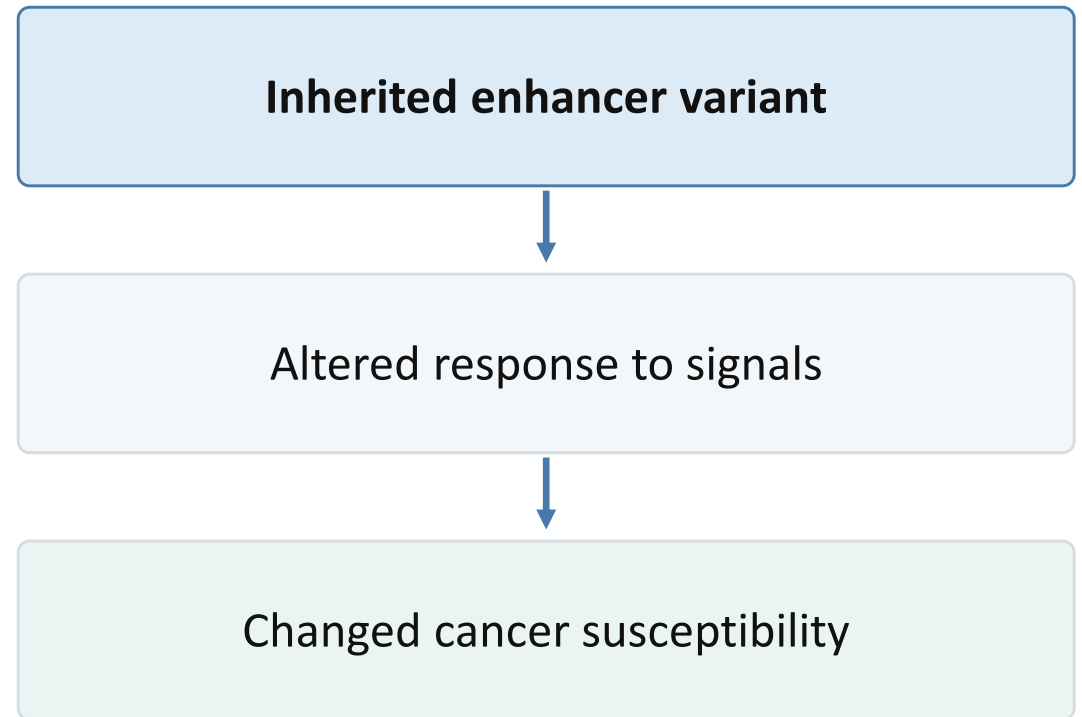
Alternative inherited regulatory alleles



Schematic: Altered responsiveness, not rearrangement

Inherited MYC-enhancer variants: Interpretation

- Examples cited include risk for prostate and ovarian cancer and certain leukemias.
- The textbook says these enhancer variants appear to raise MYC RNA responsiveness.
- No per-allele effect sizes or clinical prediction values are provided.



Mechanistic classification of MYC upregulation

Alteration	Immediate effect	Representative context
MYC translocation	Enhancer-driven expression	Burkitt lymphoma
MYC amplification	Increased gene dosage	Breast / colon / lung
NMYC or LMYC amplification	MYC-family copy gain	Neuroblastoma / small-cell lung
Upstream pathway activation	Altered transcription/translation/stability	RAS, Notch, Wnt, Hedgehog
Enhancer-risk SNP	Altered regulatory responsiveness	Inherited cancer susceptibility

Case discussion: Rapidly growing B-cell tumor

A lymphoid tumor is found to carry a rearrangement involving MYC and an immunoglobulin regulatory region.

Reasoning questions

- What mechanism increases MYC expression?
- Why can this promote rapid tumor growth?

Enhancer hijacking places MYC under potent lymphoid regulatory activity; MYC stimulates cycle and biosynthetic programs.

Case discussion: Wnt-active colon carcinoma

A colon carcinoma shows evidence of persistent Wnt signaling without an identified MYC rearrangement.

Reasoning questions

- Can MYC still be elevated?
- Where is the likely driver in the causal chain?

Yes. Upstream Wnt-pathway dysregulation can raise MYC as a downstream transcriptional effector.

Case discussion: MYC-family copy-number gain

A neuroblastoma specimen is reported to contain amplification of NMYC.

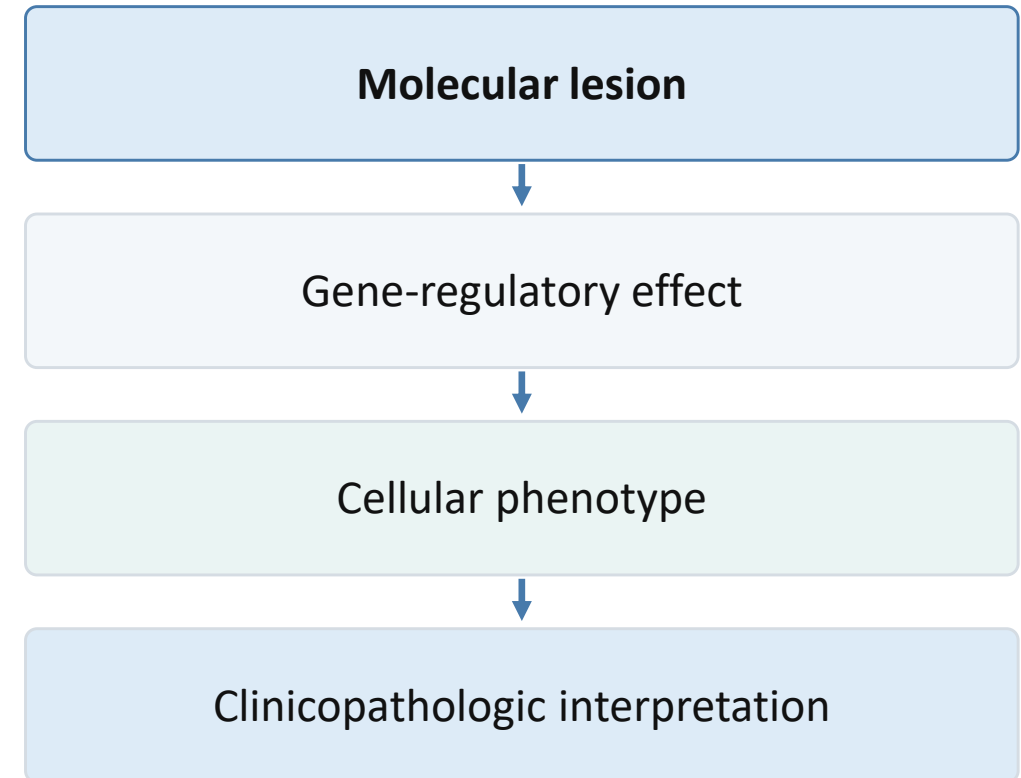
Reasoning questions

- Which oncogenic mechanism is illustrated?
- Why is this different from an MYC translocation?

Copy-number amplification of a MYC-family gene, rather than relocation beside a potent enhancer.

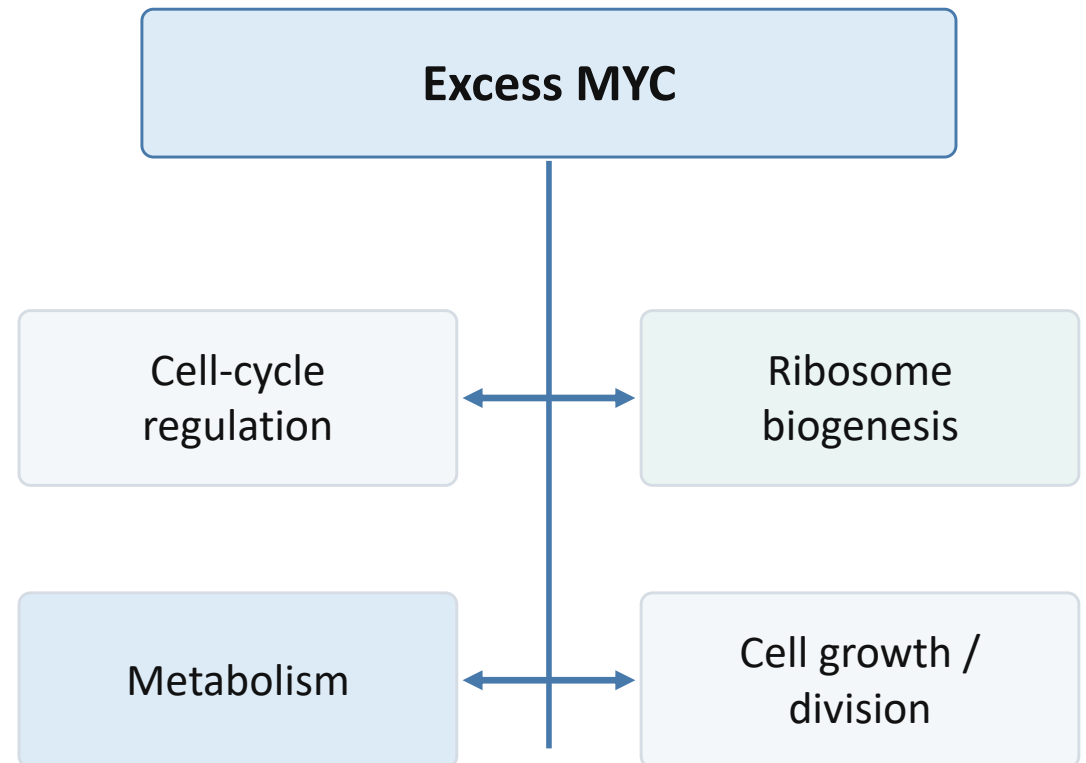
Interpretation pitfalls in molecular pathology

- High MYC expression does not identify a unique molecular cause.
- MYC rearrangement is not a standalone diagnosis without tumor context.
- The excerpt does not justify numeric biomarker thresholds or sensitivity claims.
- Stemness and telomerase effects must retain the qualifiers used by Robbins.



Integrated model of oncogenic MYC activation

- A direct MYC lesion or an altered pathway elevates MYC output.
- MYC coordinates cell-cycle, ribosomal and metabolic gene programs.
- The combined program supports neoplastic expansion.



Synthesis: Six defensible conclusions

- Mitogenic pathways converge on nuclear gene regulation.
- MYC normally rises rapidly and transiently after growth stimulation.
- MYC drives cell-cycle, ribosomal and metabolic growth programs.
- Rearrangement, amplification and upstream signaling can raise MYC.
- Some MYC effects are context-dependent or still inferential.
- A molecular mechanism is not by itself a diagnostic classification.

Textbook references

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th ed., Chapter 7: Neoplasia; Transcription Factors and MYC.
- Same textbook, Chapter 1: Transcription Factors; DNA-binding domains, promoters, enhancers and co-regulators.