

Growth-Promoting Metabolic Alterations

Cancer growth depends on rerouting nutrient carbon toward new cell material.

- Metabolic reprogramming links oncogenic signaling to biosynthesis.
- The Warburg effect is a prominent, but not cancer-specific, example.
- Glucose, glutamine, mitochondria, and tumor suppressors act as one system.

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

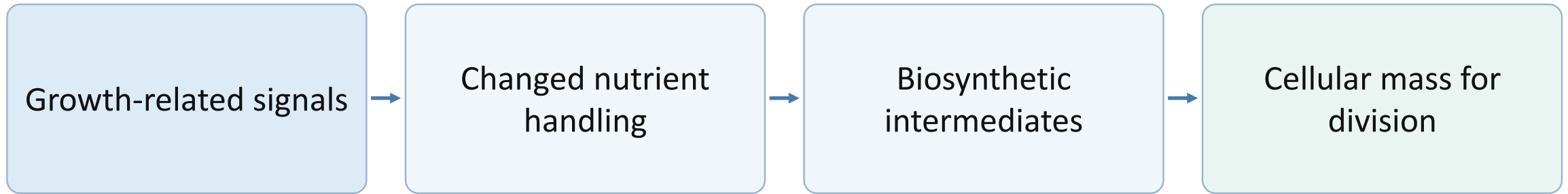
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Learning outcomes

- Define aerobic glycolysis and explain why oxygen does not suppress it in growing cells.
- Contrast ATP production with the need for biosynthetic carbon intermediates.
- Trace how RTK–PI3K–AKT, MYC, STK11 and p53 reshape metabolism.
- Interpret FDG-PET avidity and inherited Krebs-cycle tumor-suppressor defects.

Metabolism becomes a growth program

Molecular basis of cancer: An altered cellular phenotype



- Malignant cells exploit a metabolic program also used by rapidly growing normal tissues.
- Mutations favor sustained activation of a program normally linked to controlled growth.

Warburg effect: The defining phenotype

High glucose uptake and glycolytic fermentation despite available oxygen.

- The presence of oxygen does not necessarily shift the cell to maximal glucose oxidation.
- Cancer cells often convert substantial glucose-derived carbon to lactate.
- This pattern is called aerobic glycolysis.

Aerobic glycolysis is not oxygen deprivation

Aerobic glycolysis

- Oxygen is available to the cell.
- Glucose is avidly taken up.
- Fermentative glycolysis remains prominent.

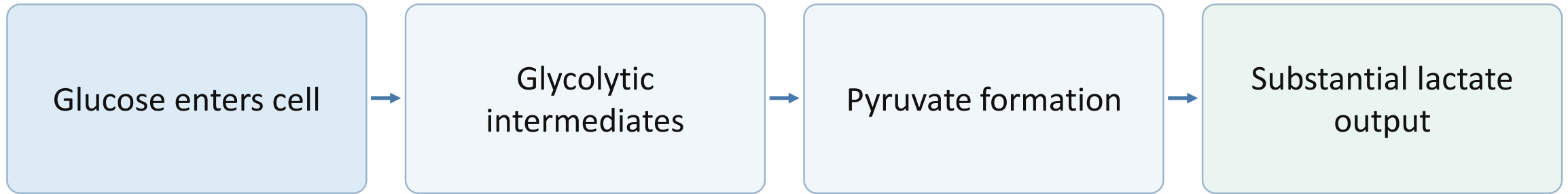
True oxygen limitation

- Insufficient oxygen constrains respiratory metabolism.
- Glycolysis can sustain some ATP production.
- Do not equate these distinct causes of lactate production.

The word “aerobic” describes oxygen availability, not exclusive mitochondrial respiration.

What happens to incoming glucose?

Simplified carbon-fate schematic



- Rapid glucose uptake can accompany growth even in oxygen-rich conditions.
- Some intermediates branch from the pathway to support anabolism.

Increased glucose uptake has a purpose

- Growth demands a sustained supply of intracellular carbon molecules.
- Glycolysis provides both usable energy and intermediate compounds.
- Transport and enzyme activity are increased by progrowth signaling.
- Glucose avidity is a metabolic behavior—not a stand-alone cancer diagnosis.

The Warburg effect is not cancer-specific

Growing normal cells

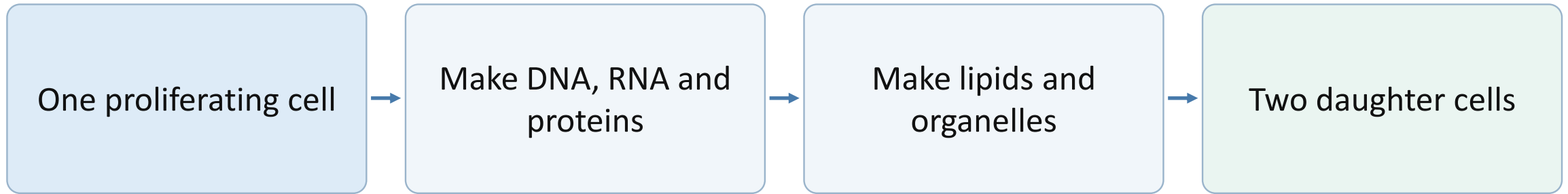
- Embryonic and other proliferating tissues can adopt aerobic glycolysis.
- Growth signals normally regulate the transition.
- Biosynthetic needs drive the pattern.

Cancer cells

- Similar anabolic metabolism is often sustained.
- Oncogenic mutations deregulate its control.
- The phenotype is common, not exclusive to malignancy.

Cell division imposes a mass-balance requirement

Before one cell becomes two, its contents must be duplicated



- A cell cannot divide successfully by generating ATP alone.
- Biosynthesis requires retaining and redirecting nutrient carbon.

Energy production versus precursor generation

Catabolic emphasis

- Oxidize fuel to harvest energy.
- Complete glucose oxidation releases carbon as CO₂.
- Efficient ATP output does not itself build biomass.

Anabolic emphasis

- Preserve carbon in useful intermediate pools.
- Route carbon into nucleic acids, proteins and lipids.
- Supply molecular components for cell growth.

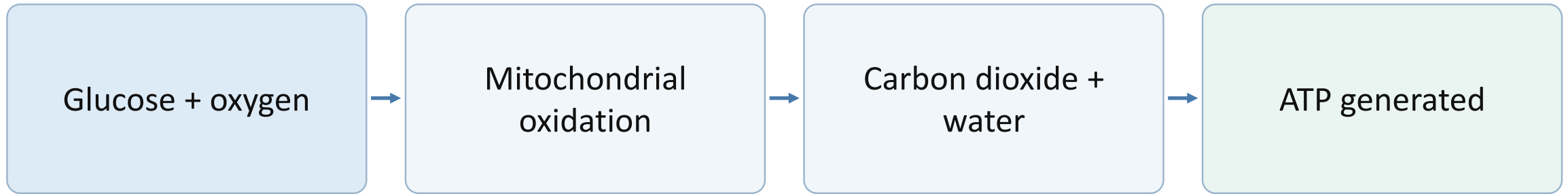
Proliferation requires energy AND substrates for macromolecules.

Two contrasting fates of glucose carbon

Feature	Complete oxidation	Growth-directed metabolism
Primary emphasis	Energy generation	Energy plus biomass precursors
Carbon fate	Much is ultimately lost as CO ₂	A fraction is retained in intermediates
Growth utility	Supports ATP requirements	Supports macromolecule production
Key point	Not sufficient alone for division	Compatible with rapid proliferation

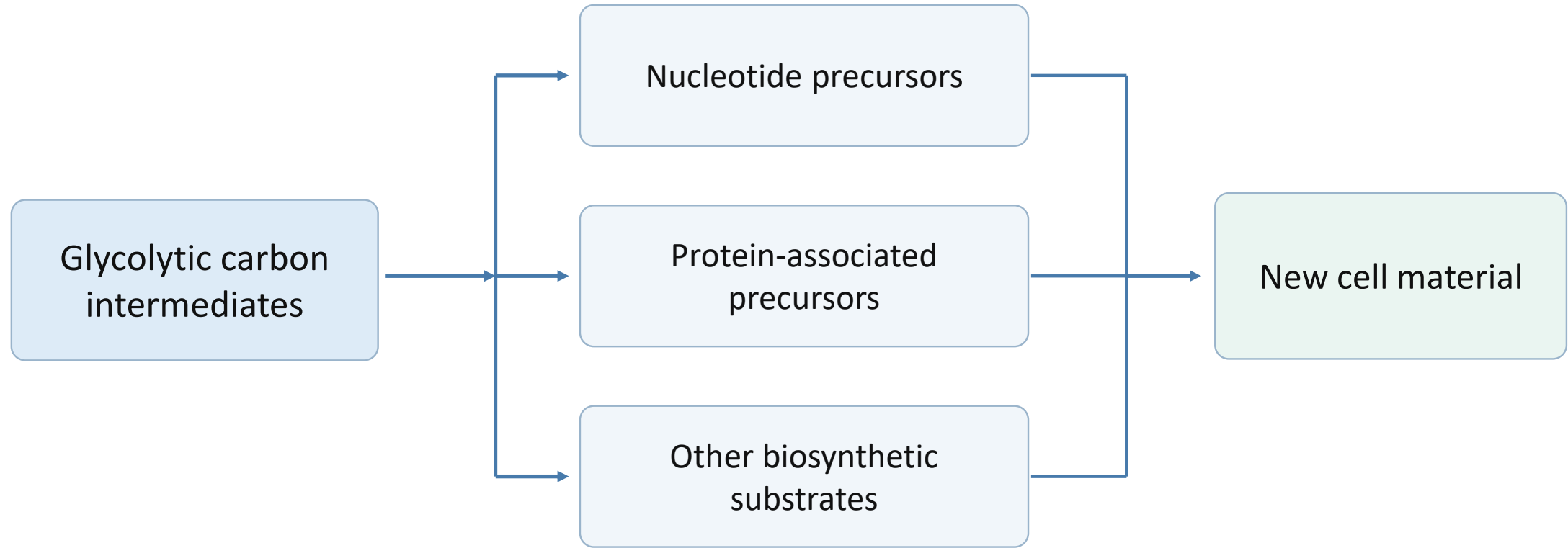
Why complete oxidation loses usable carbon

Simplified net reaction highlighted



- Complete oxidation extracts energy but releases glucose-derived carbon as CO₂.
- Those carbon atoms can no longer be incorporated into cellular building blocks.

Diversion points support biosynthesis



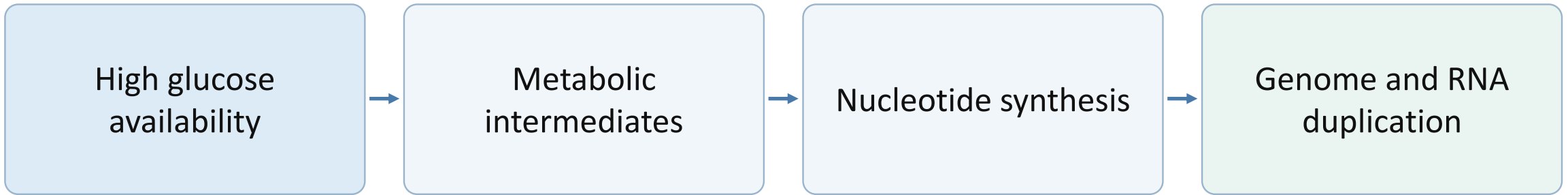
The advantage is access to molecular precursors, not maximal ATP per glucose.

Nucleic acids require new carbon

- Cell replication requires additional DNA and RNA.
- Carbon intermediates derived from central metabolism support nucleotide synthesis.
- Diverting intermediates away from complete oxidation helps meet this demand.
- The textbook links these needs to glycolytic precursor pools.

DNA/RNA synthesis is part of the growth logic

Conceptual link; Not a detailed biochemical pathway



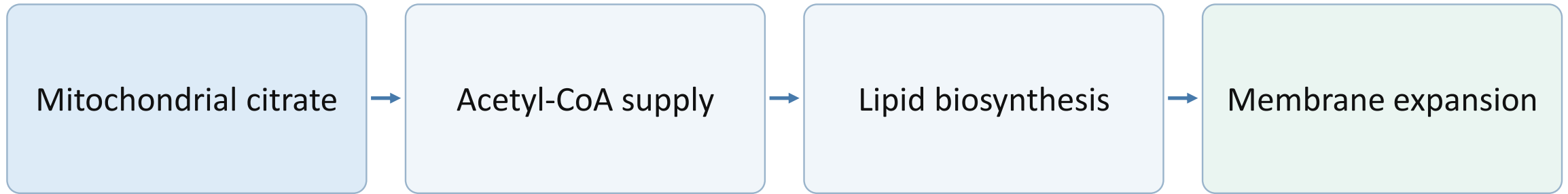
- A proliferating cell requires chemical precursors as well as replication machinery.
- The metabolic phenotype helps sustain this biosynthetic burden.

Protein synthesis creates another demand

- Expanding cell mass requires synthesis of many proteins.
- Growth signals coordinate metabolic substrate availability with protein production.
- Carbon is retained in cellular constituents rather than converted exclusively to CO₂.
- PI3K/AKT signaling also stimulates factors required for protein synthesis.

Lipids are needed for membrane expansion

Citrate links mitochondrial metabolism to cytoplasmic lipid biosynthesis



- Acetyl-CoA is essential for lipid synthesis.
- Citrate generated in mitochondria as a major upstream source.

Organelle duplication is a metabolic task

- Division entails reproduction of cellular structures, not just chromosomal DNA.
- Organelle growth consumes proteins, lipids, and other macromolecules.
- A growth-supporting metabolic network must provide multiple precursor classes.
- The resulting demand explains why metabolism is integrated with proliferation.

What must a growing cell manufacture?

Cellular component	Biosynthetic demand	Metabolic implication
DNA and RNA	New nucleic acids	Reserve suitable carbon intermediates
Proteins	Expanded protein mass	Coordinate precursors and synthesis machinery
Lipids	New membrane material	Supply citrate-derived acetyl-CoA
Organelles	Cellular structural material	Coordinate multiple synthetic pathways

ATP efficiency is not the only optimum

The best metabolic state for division need not maximize ATP per glucose molecule.

- Aerobic glycolysis appears energetically inefficient in isolation.
- Its intermediate pools provide substrate for biosynthetic pathways.
- Tumor growth selects for an appropriate balance of energy and carbon supply.

How ATP yields

Pathway scenario	Textbook value	Interpretation
“Pure” glycolysis	2 ATP / glucose	Limited ATP, useful metabolite intermediates
Complete oxidative phosphorylation	36 ATP / glucose	Historical textbook comparison
Growth-associated mixed metabolism	~4 ATP / glucose (average)	Represents mixed glycolytic/oxidative flux

Illustrative textbook values are not universal fixed cellular yields.

The metabolic “sweet spot”

Why glycolysis stays prominent

- Supports access to biosynthetic intermediates.
- Maintains rapid uptake of glucose.
- Provides some ATP directly.

Why respiration remains relevant

- Growing cells still use mitochondria.
- The Krebs cycle supplies biosynthetic precursors.
- Mixed metabolism can better support mass production.

Warburg metabolism does not abolish mitochondria

Growing cancer cells can be highly glycolytic and still depend on mitochondrial metabolism.

- Mitochondria provide pathways for generating biosynthetic intermediates.
- The Krebs cycle remains important even when fermentation is prominent.
- A simple “glycolysis ON / mitochondria OFF” model is inaccurate.

Quiescent and growing cells use carbon differently

Quiescent cell

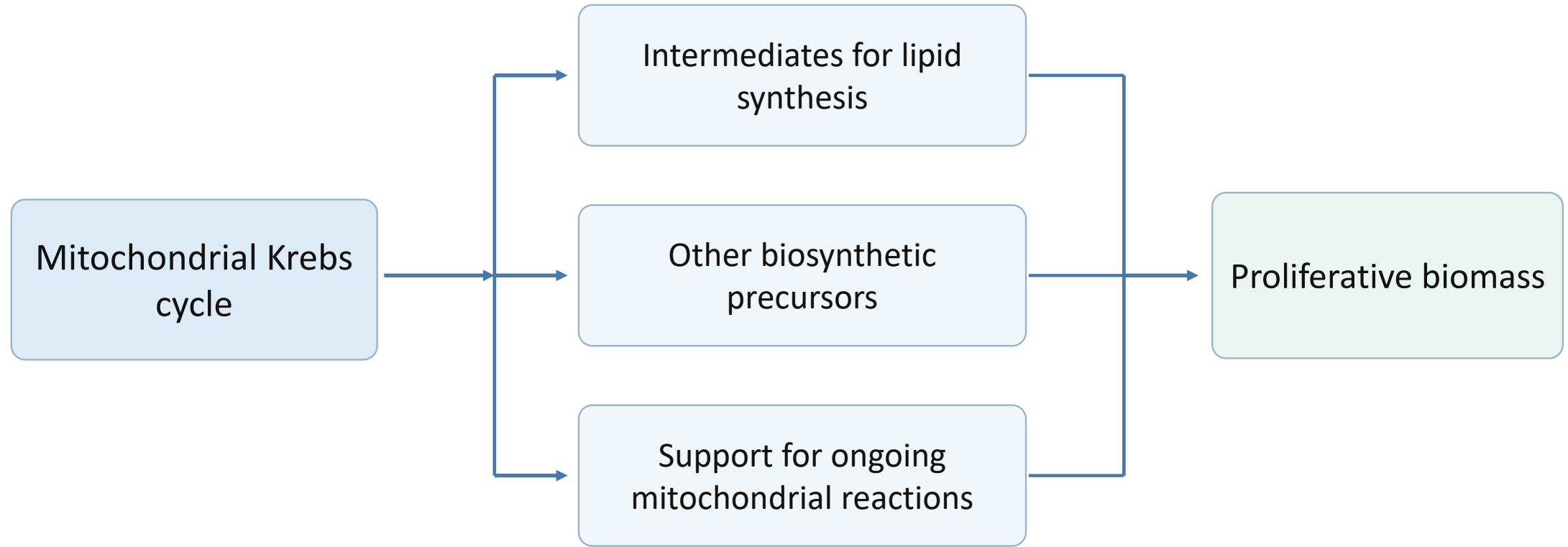
- Energy maintenance is a major priority.
- The Krebs cycle supports ATP generation.
- Macromolecules still require some precursor supply.

Growing cell

- Glucose and glutamine uptake rise.
- Intermediate production is redirected into anabolism.
- Nucleotides, proteins and lipids are assembled.

Cellular state changes how metabolism is allocated.

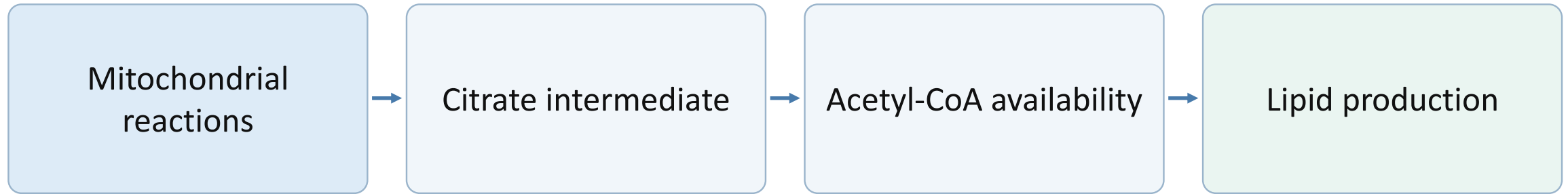
The Krebs cycle is a biosynthetic hub



The text stresses carbon-intermediate generation as a major growth-related role.

Citrate connects two metabolic compartments

A selected example from the Robbins mechanism



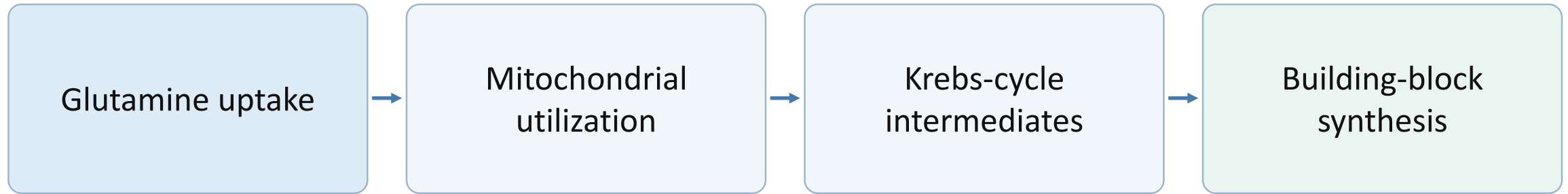
- Citrate produced during mitochondrial metabolism supports lipid anabolism.
- The diagram summarizes a functional connection, not every reaction in the pathway.

Acetyl-CoA and lipid biogenesis

- Acetyl coenzyme A supplies carbon used during lipid biosynthesis.
- In growing cells, mitochondrial citrate is a major source upstream of acetyl-CoA.
- The anabolic requirement helps explain mitochondrial activity during the Warburg state.
- Metabolic carbon allocation connects growth signaling to membrane synthesis.

Glutamine contributes carbon to mitochondrial metabolism

Substrate entry is shown conceptually



- A large fraction of carbon entering mitochondrial pathways can derive from glutamine.
- Growing cells therefore require glutamine uptake in addition to glucose uptake.

Glucose and glutamine are complementary fuels

Glucose

- Strongly increased uptake in many growing cells.
- Supports glycolytic precursors.
- Helps supply ATP and anabolic carbon.

Glutamine

- Important entry source for mitochondrial metabolism.
- Supports Krebs-cycle intermediate pools.
- Used to furnish cellular building blocks.

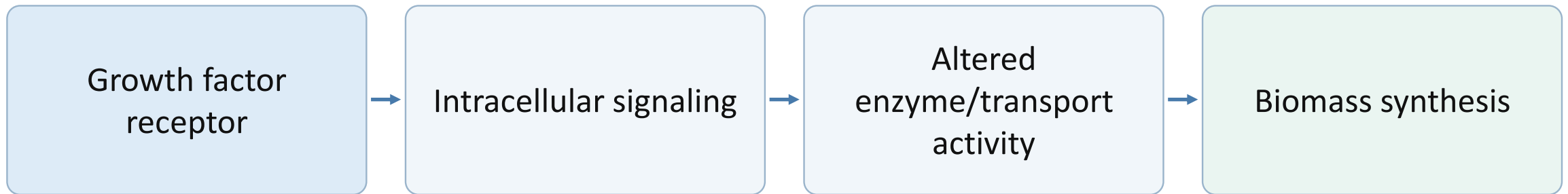
Growth cannot be understood by considering glucose alone.

A compartment-level account of growth metabolism

Location / process	Main role in this lecture	Important output
Glucose uptake	Increase substrate availability	Carbon enters cytoplasmic pathways
Glycolysis	Produce intermediates and some ATP	Precursors for biosynthesis
Mitochondrial Krebs cycle	Generate useful carbon intermediates	Citrate and other precursors
Biosynthetic pathways	Assemble cellular constituents	DNA, RNA, proteins, lipids

Growth-factor signaling initiates reprogramming

Normal cells coordinate growth signals and metabolic output



- Progrowth signaling links substrate availability to the decision to divide.
- This response is regulated and transient in normal proliferating cells.

Normal control versus oncogenic persistence

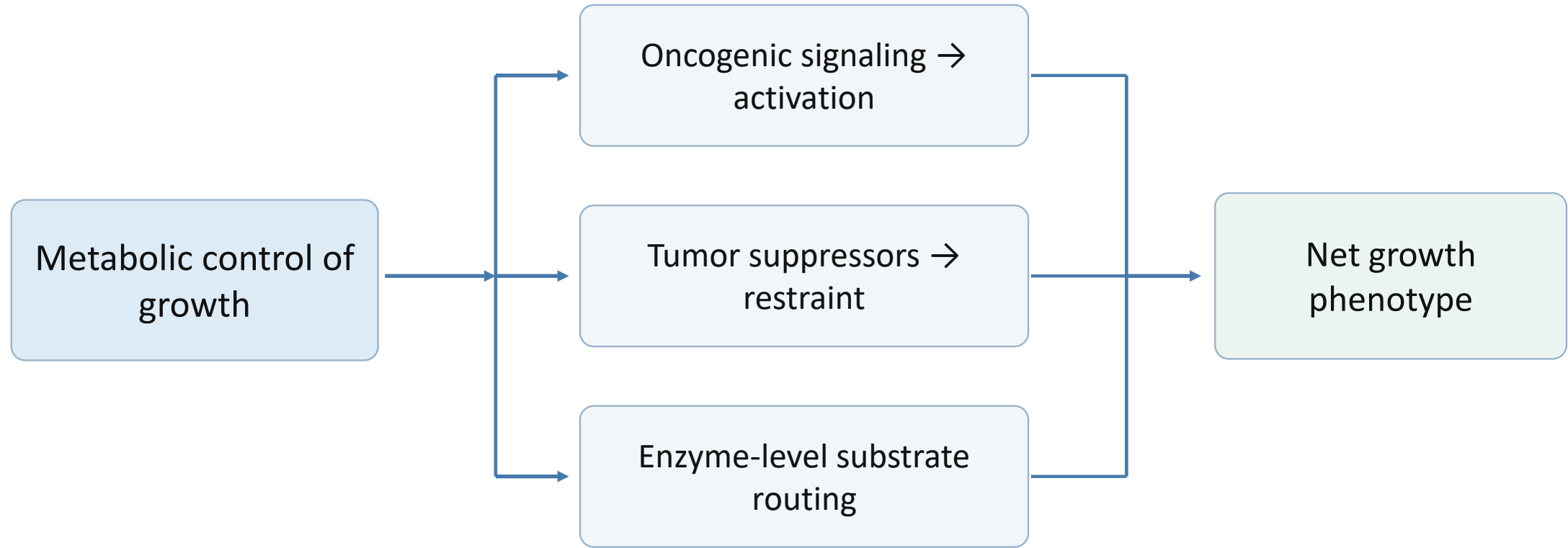
Physiologic control

- Growth signals regulate metabolism.
- Anabolic activity follows proliferation needs.
- Regulatory pathways can restrain the state.

Cancer-associated deregulation

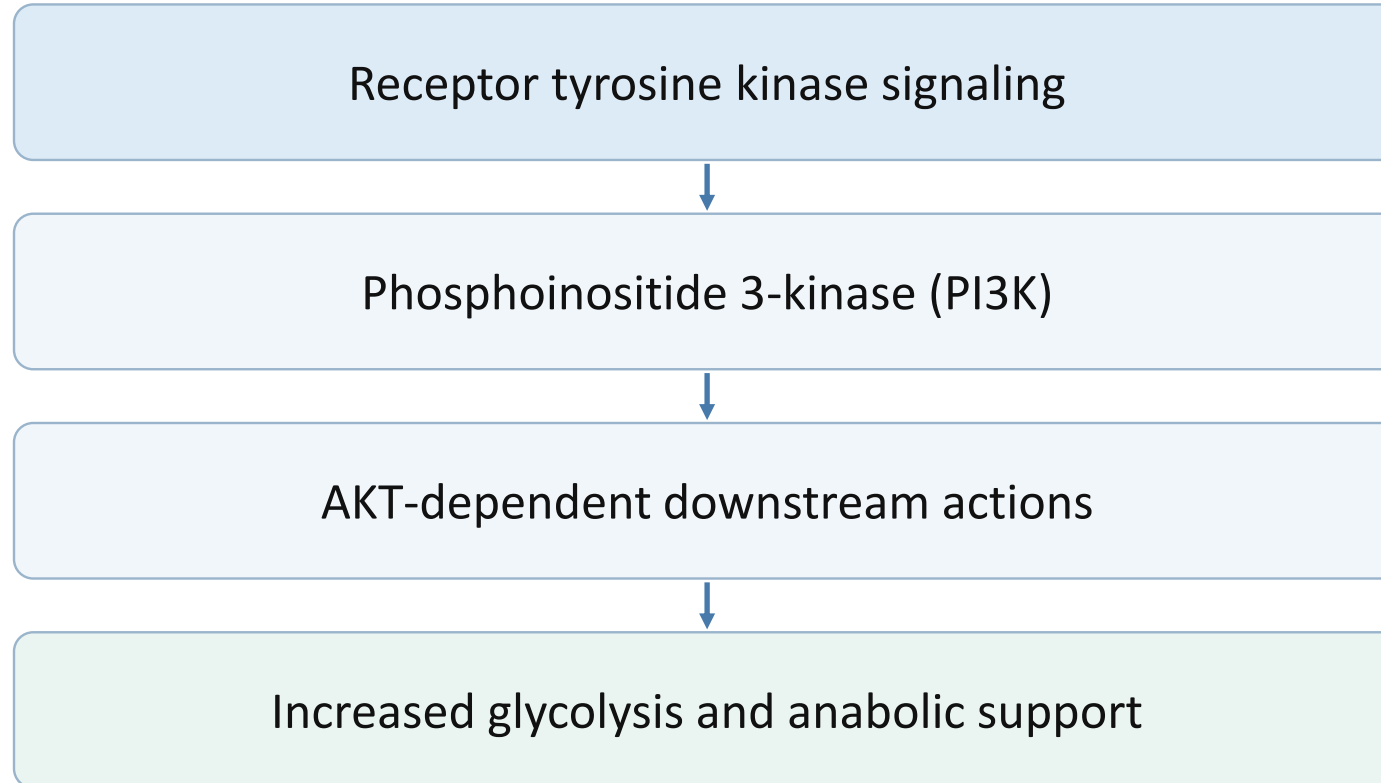
- Oncogenes favor ongoing metabolic activation.
- Loss of tumor-suppressor function weakens restraints.
- Growth-promoting metabolism persists.

Two opposing classes of regulatory genes



The Warburg phenotype emerges from integrated control, not one enzyme alone.

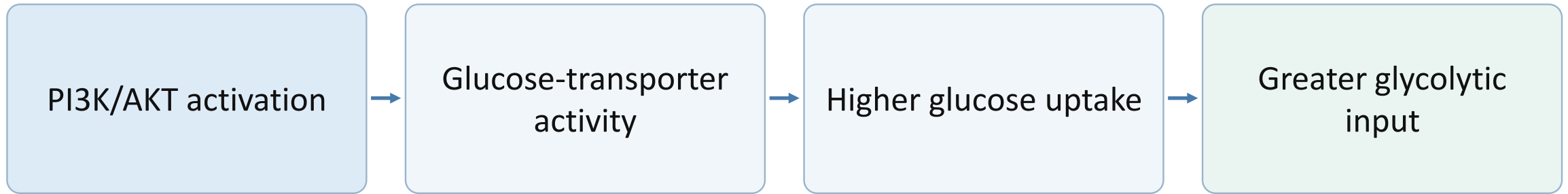
RTK–PI3K–AKT is a metabolic switch



This cascade coordinates transport, metabolic enzymes, lipid synthesis and protein synthesis.

AKT signaling increases glucose transport

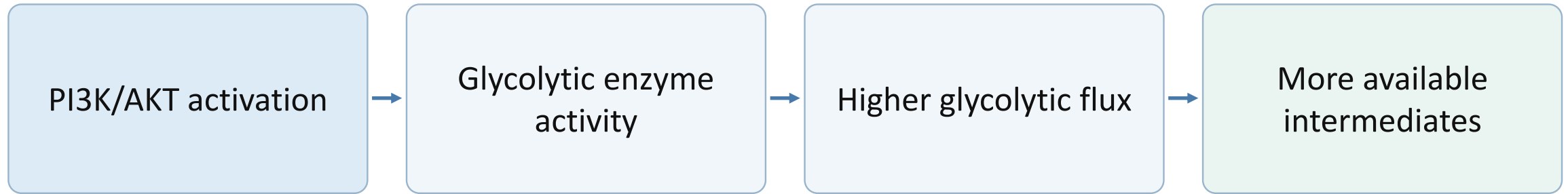
One major output of the pathway



- Increased glucose-transporter activity downstream of PI3K/AKT.
- A larger substrate supply supports carbon-intensive cell growth.

AKT signaling stimulates glycolytic enzymes

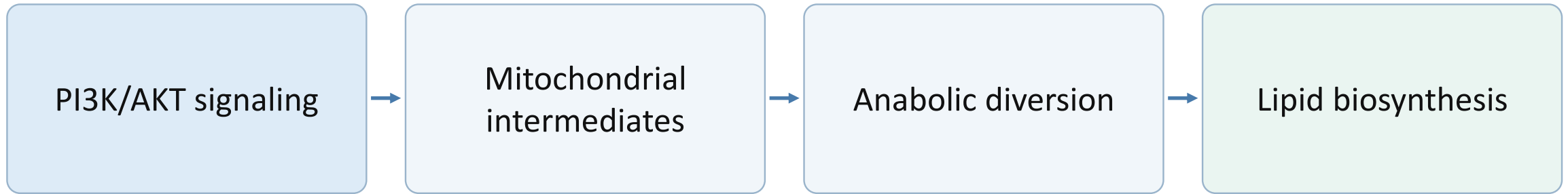
Another major output of the pathway



- Transporter changes and enzyme changes reinforce each other.
- Increased pathway activity can feed energy generation and precursor production.

AKT favors lipid-directed mitochondrial carbon

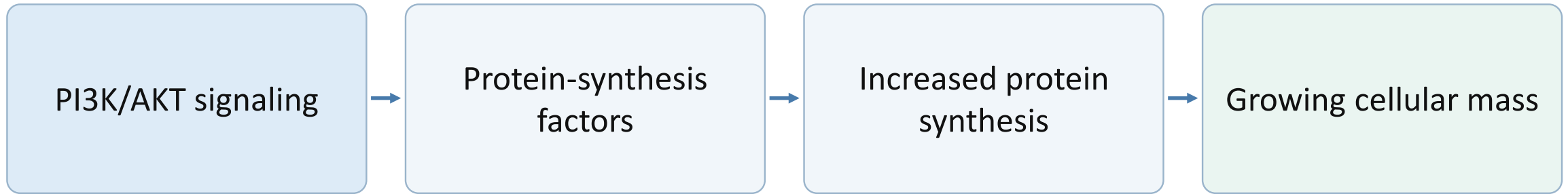
Metabolic routing is coupled to growth signaling



- Mitochondrial products can be redirected toward lipids rather than fully oxidized.
- This coupling supplies material for membrane expansion.

AKT also supports protein production

Metabolic reprogramming extends beyond glycolysis



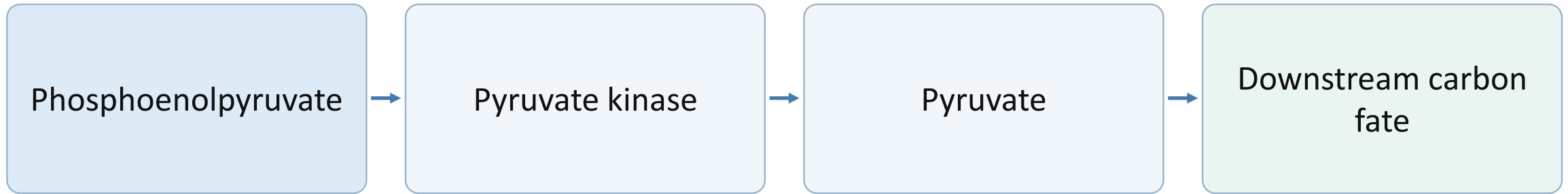
- Protein synthesis is a coordinated output of progrowth signaling.
- Nutrient capture alone would not produce a larger cell without synthetic machinery.

PI3K/AKT acts at several metabolic levels

Level	Action described in Robbins	Growth consequence
Transport	Upregulates glucose transporters	More carbon substrate
Metabolism	Increases glycolytic enzymes	More glycolytic processing
Carbon allocation	Promotes diversion to lipid synthesis	Membrane building blocks
Synthesis machinery	Stimulates protein-synthesis factors	Greater protein production

Pyruvate kinase normally completes glycolysis

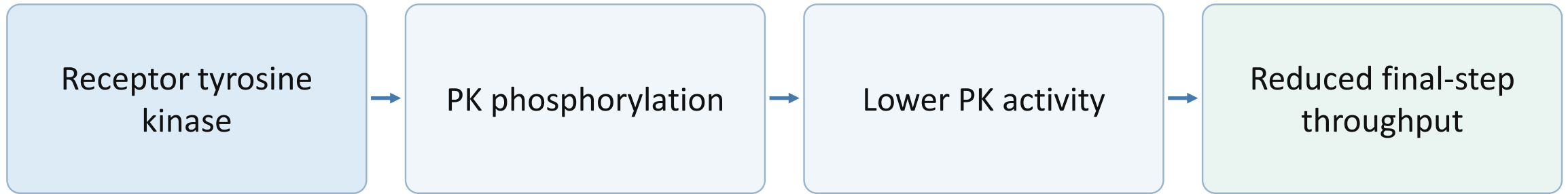
Final glycolytic step highlighted in the source



- Pyruvate kinase catalyzes conversion of phosphoenolpyruvate to pyruvate.
- The textbook uses this step to illustrate how signaling redirects glycolytic intermediates.

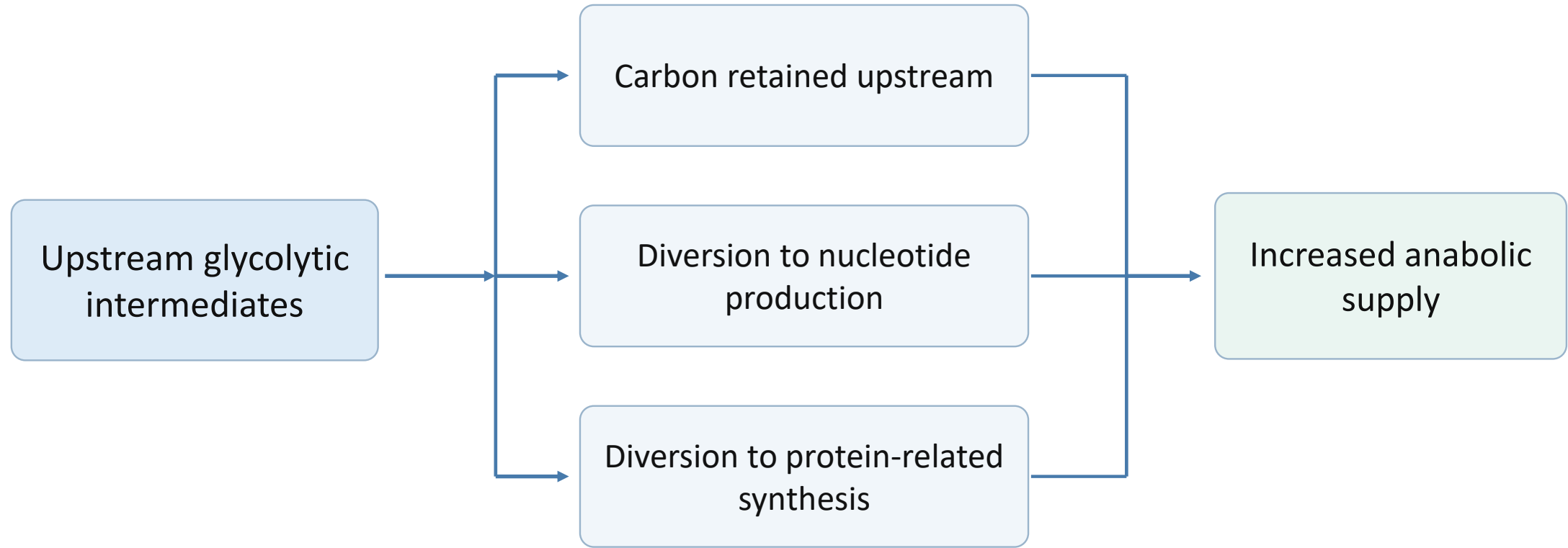
RTK signaling can inhibit pyruvate kinase

Specific enzyme-level checkpoint



- Phosphorylation-associated inhibition of pyruvate kinase.
- This can restrain conversion of phosphoenolpyruvate into pyruvate.

An upstream bottleneck creates a precursor pool



This is the “damming effect” described for pyruvate-kinase inhibition.

Why slowing one reaction can favor cell growth

Without the bottleneck

- The terminal step converts upstream substrate toward pyruvate.
- Less accumulation occurs at that control point.
- Flux distribution favors downstream passage.

With PK inhibition

- Earlier metabolites accumulate.
- A larger upstream pool can feed branch pathways.
- The effect supports biosynthesis despite slower final-step flux.

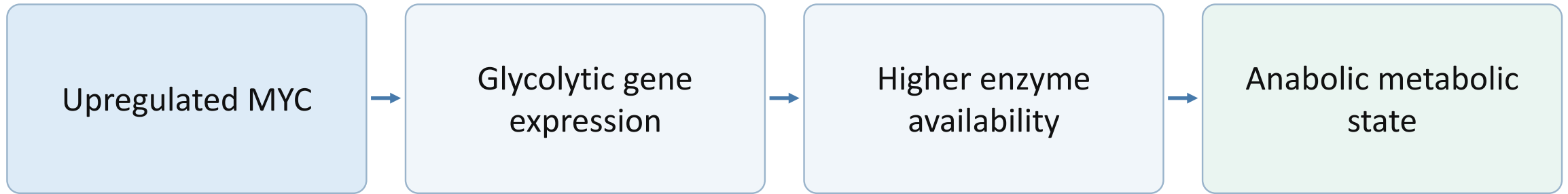
MYC coordinates an anabolic transcriptional program

MYC drives gene-expression changes that favor biosynthesis and cell growth.

- Progrowth pathways upregulate the transcription factor MYC.
- MYC increases expression of multiple glycolytic enzymes.
- MYC also upregulates glutaminase, supporting glutamine use by mitochondria.

MYC increases glycolytic capacity

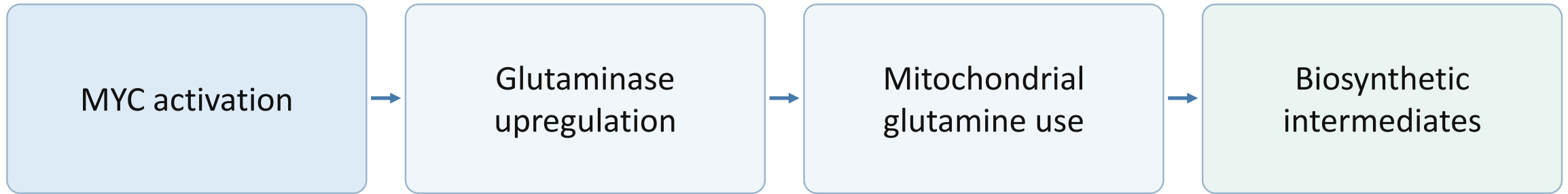
Gene regulation translates into metabolic activity



- MYC contributes to the sustained glycolytic phenotype of growing cells.
- Regulation occurs at the level of transcription as well as signal-induced enzyme activity.

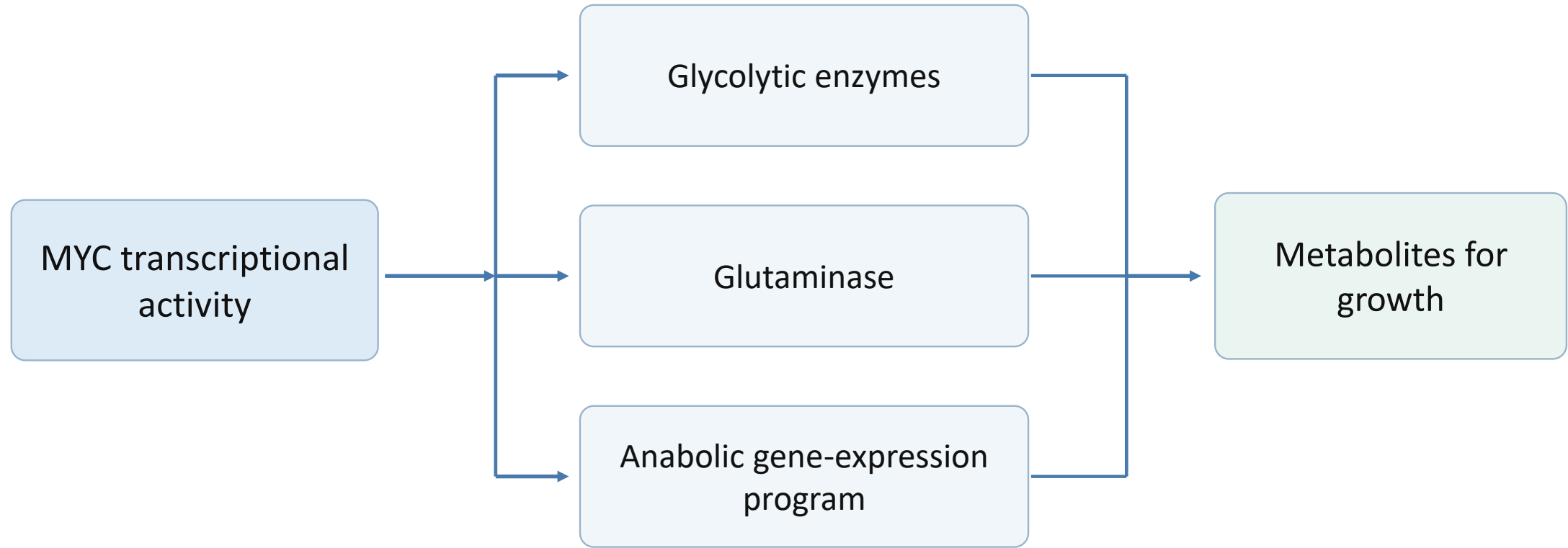
MYC increases glutaminase expression

The glutamine arm of metabolic growth



- Glutaminase is needed for the mitochondrial utilization of glutamine described in the text.
- The gene-expression program supports more than glucose metabolism.

MYC unites two carbon-input programs



MYC connects nutrient handling with the cell's increased synthetic burden.

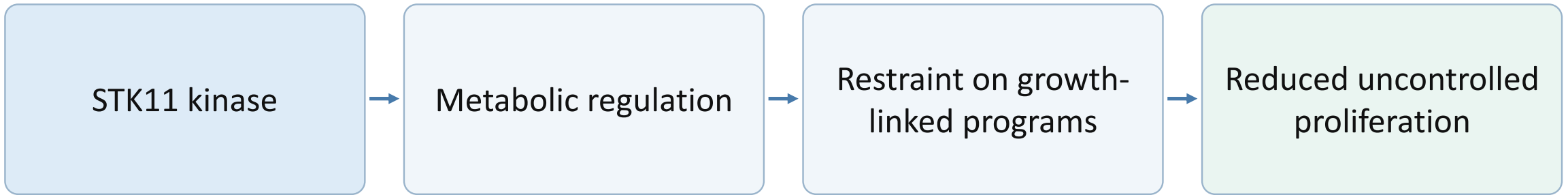
Tumor suppressors restrain anabolic metabolism

Growth arrest and metabolic restraint are closely intertwined.

- Cancer-associated metabolic activation is not exclusively caused by oncogene gain.
- Tumor suppressors oppose pathways that support glucose use and anabolism.
- Loss of tumor-suppressor activity permits sustained growth-promoting metabolism.

STK11/LKB1 acts as a metabolic regulator

Established parent context on the same textbook page



- STK11 affects glucose handling, protein synthesis, mitochondrial biology and lipids.
- The source identifies its normal function as opposing Warburg-associated changes.

STK11 has hereditary and somatic relevance

Germline STK11 loss

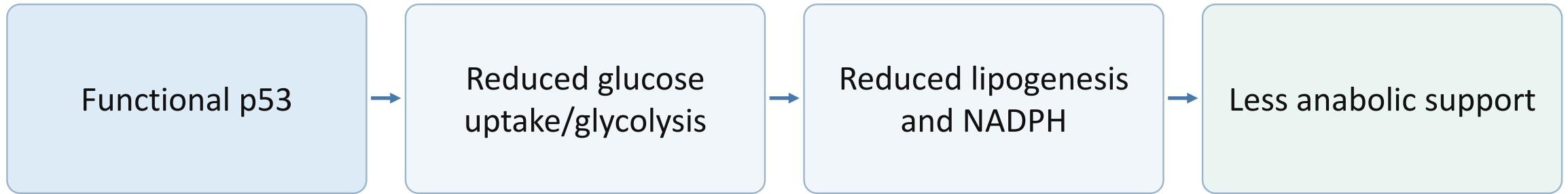
- Causes Peutz–Jeghers syndrome.
- Associated with gastrointestinal polyps.
- Increases risk for multiple epithelial cancers.

Somatic STK11 loss

- Occurs in diverse carcinomas.
- Demonstrates that metabolic control can be altered during tumor evolution.
- Links a tumor-suppressor defect to growth-supporting metabolism.

P53 is a broad metabolic counterweight

Several opposing effects



- The metabolic targets are described collectively rather than as one isolated switch.
- These inhibitory effects complement p53-mediated restraint of proliferation.

Why NADPH matters for anabolism

- NADPH is a cofactor needed in biosynthesis of macromolecules.
- P53 represses processes contributing to NADPH generation.
- Reducing reductive biosynthetic capacity can constrain cell growth.
- NADPH control is one facet of the broader p53 metabolic program.

Cancer gene products and metabolic direction

Regulator	Direction emphasized	Principal metabolic effect
PI3K/AKT	Promotes anabolic state	Glucose uptake, glycolysis, lipid/protein synthesis
MYC	Promotes anabolic state	Glycolytic enzymes and glutaminase
STK11	Opposes growth-linked state	Broad cellular metabolic restraint
p53	Opposes growth-linked state	Restricts glycolysis, lipids and NADPH

Some Krebs-cycle enzymes are tumor suppressors

Loss of certain metabolic enzymes can predispose to neoplasia.

- The source identifies fumarate hydratase (FH) and succinate dehydrogenase (SDH).
- Germline loss-of-function mutations are associated with inherited tumor risks.
- The mechanisms connecting impaired Krebs-cycle function to transformation are incompletely resolved.

FH and SDH: Inherited neoplastic associations

FH (fumarate hydratase)

- Encodes a Krebs-cycle enzyme.
- Germline loss-of-function mutations predispose to tumors.
- Renal cell carcinoma is among the associated tumor types noted.

SDH (succinate dehydrogenase)

- Encodes a Krebs-cycle enzyme.
- Inherited loss-of-function creates tumor susceptibility.
- Pheochromocytoma is among the associated tumor types noted.

The examples are associations noted by Robbins—not an exhaustive syndrome classification.

Why can impaired Krebs-cycle activity promote cancer?

Proposed mechanism 1

- Krebs-cycle inhibition may favor a glycolytic growth phenotype.
- Altered carbon routing could reinforce Warburg metabolism.
- The source presents this as a hypothesis.

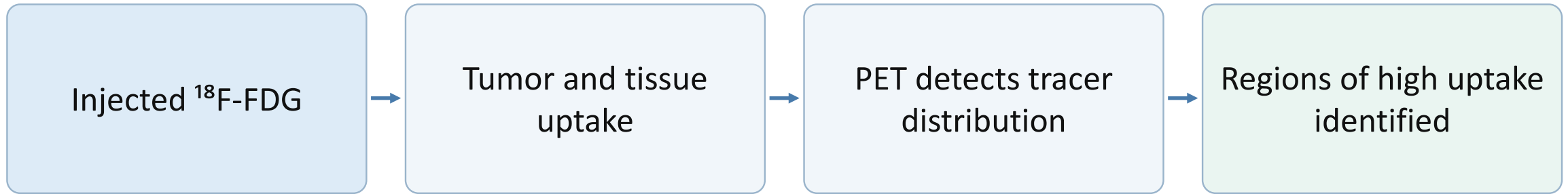
Proposed mechanism 2

- Abnormal metabolites may exert oncogenic effects.
- Such molecules are termed oncometabolites.
- The detailed mechanisms belong to the adjacent oncometabolism topic.

The precise mechanism remains uncertain.

FDG-PET exploits elevated glucose uptake

Clinical translation of a common cancer metabolic phenotype



- ^{18}F -fluorodeoxyglucose is a glucose analog used as a PET tracer.
- The result reflects glucose avidity and is not uniquely specific for cancer.

FDG accumulation is not restricted to tumors

Tumor-associated avidity

- Many tumors are FDG-PET positive.
- Rapidly growing tumors are often strongly avid.
- Uptake is consistent with increased glucose handling.

Normal proliferating tissues

- Active bone marrow may also take up tracer.
- Normal tissue uptake can coexist with tumor uptake.
- Interpretation needs appropriate clinical context.

What FDG-PET can and cannot establish

Finding	Reasonable inference	Unwarranted inference
High FDG uptake	Increased glucose-avid activity	Definitive malignancy on metabolism alone
Tumor with strong avidity	A metabolic phenotype compatible with high growth	Specific oncogene mutation identified
Bone marrow tracer uptake	Normal actively dividing tissue may contribute	Every focus is a metastatic deposit

Clinical application: A glucose-avid mass

A rapidly growing mass shows pronounced ^{18}F -FDG uptake before the tissue diagnosis is established.

Question

Which metabolic property could explain the finding?

Reasoned interpretation

High glucose uptake is compatible with aerobic glycolysis. FDG avidity alone does not establish malignancy or histologic type.

Mechanism application: A glycolytic bottleneck

A cancer cell receives strong receptor tyrosine kinase signaling that phosphorylates and inhibits pyruvate kinase.

Question

Why might precursor synthesis increase rather than decrease?

Reasoned interpretation

Reduced terminal glycolytic throughput permits upstream intermediates to accumulate and be diverted toward biosynthesis.

Mechanism application: Loss of a Krebs-cycle enzyme

A hereditary loss-of-function mutation affects FH or SDH in a patient with increased tumor susceptibility.

Question

Can this be explained solely by reduced ATP generation?

Reasoned interpretation

No. The source suggests Warburg-type shifts and abnormal-metabolite effects; The precise oncogenic mechanism remains uncertain.

Integrated mechanism: Substrate to proliferation

Control point	Metabolic consequence	Growth relevance
Glucose uptake	Larger substrate input	Supports anabolic precursor supply
Glycolytic regulation	Intermediates diverted	Nucleotides and other cell constituents
Glutamine use	Mitochondrial precursor supply	Supports multiple biosynthetic pathways
Oncogene/tumor-suppressor balance	Persistent anabolic program	Promotes uncontrolled cell growth

Five examinable mechanistic conclusions

- The Warburg effect is aerobic glycolysis—not proof of absent oxygen.
- Its growth advantage lies in biosynthetic precursor production.
- Mitochondria and glutamine remain central to proliferative metabolism.
- PI3K/AKT and MYC promote, whereas STK11 and p53 oppose, this state.
- ^{18}F -FDG uptake demonstrates glucose avidity, not cancer specificity.

Four traps in interpreting metabolic reprogramming

A single metabolic observation rarely defines the whole cancer phenotype.

- Aerobic glycolysis does not imply that mitochondria are nonfunctional.
- High FDG uptake does not establish a diagnosis of malignancy.
- Low ATP yield per glucose does not make a pathway disadvantageous for growth.
- FH or SDH loss is associated with tumor risk, but its mechanism is not fully settled.