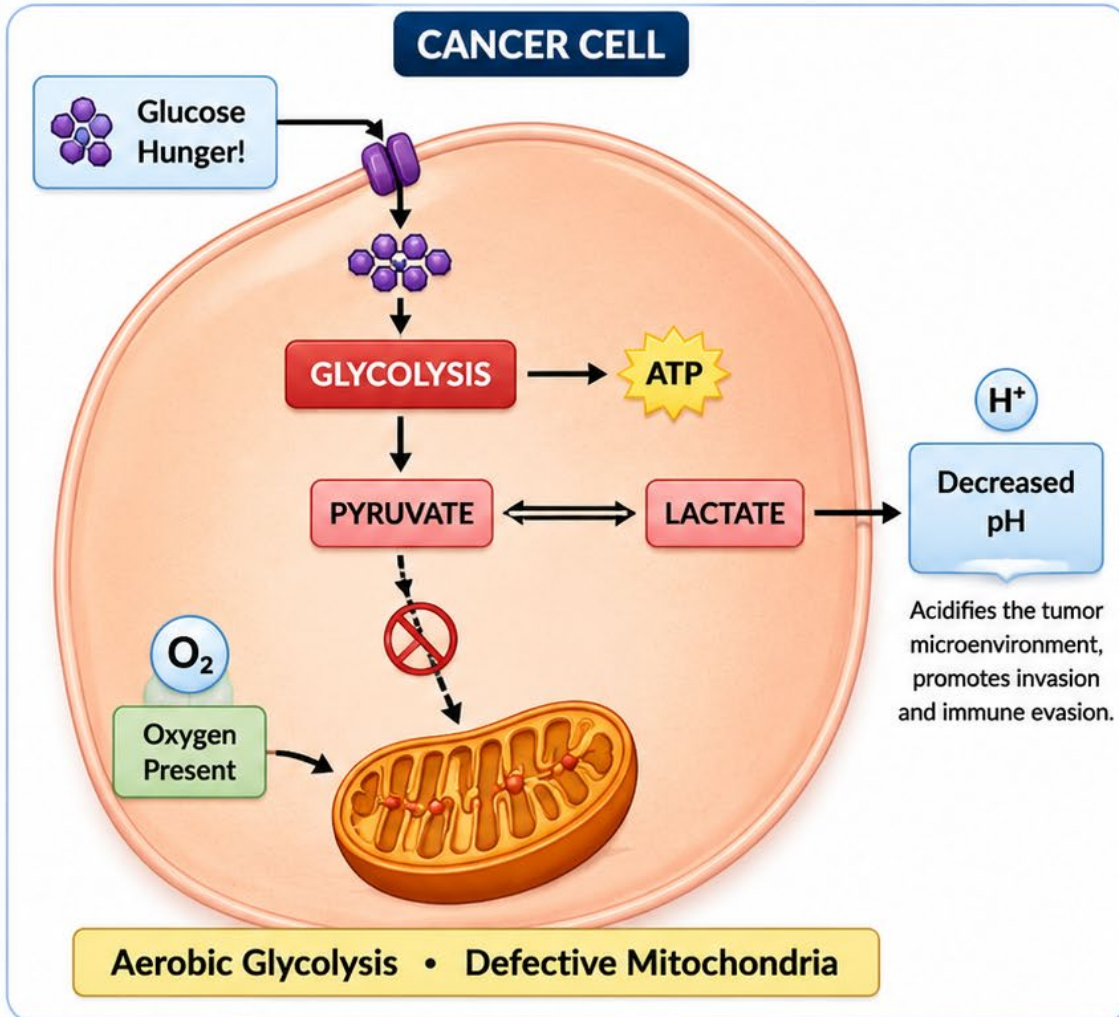


The Warburg Effect

Cancer cells preferentially use aerobic glycolysis (glucose → lactate) even in the presence of oxygen.



OTTO WARBURG, MD, PHD



“The prime cause of cancer is the replacement of the respiration of oxygen in normal body cells by a fermentation of sugar.

– Otto Warburg



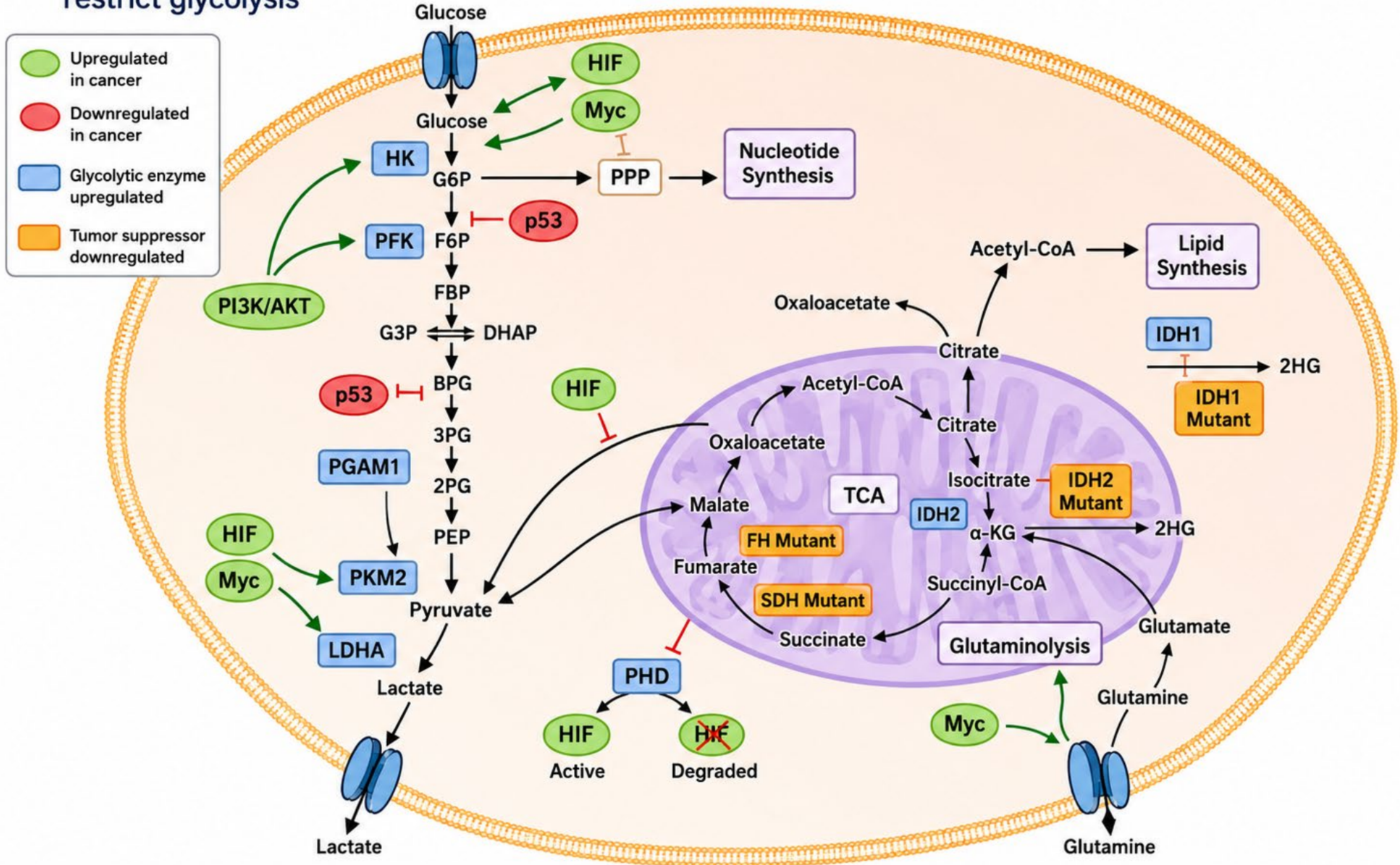
NOBEL PRIZE
in Physiology or
Medicine in 1931



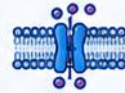
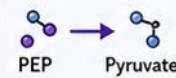
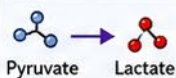
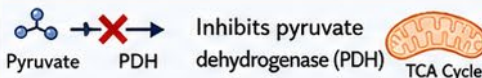
KEY POINTS

- Cancer cells consume large amounts of glucose.
- They convert most glucose to lactate through glycolysis, even when oxygen is available.
- Mitochondrial respiration is reduced or defective in many cancers.
- Lactate production leads to decreased pH, supporting tumor growth and spread.

The Warburg effect is characterized by metabolic reprogramming in cancer cells, favoring glycolysis over oxidative phosphorylation even under aerobic conditions. This shift involves **upregulation of glycolytic enzymes** and **downregulation of tumor suppressors** that normally restrict glycolysis



Key Enzymes and Regulators in the Warburg Effect

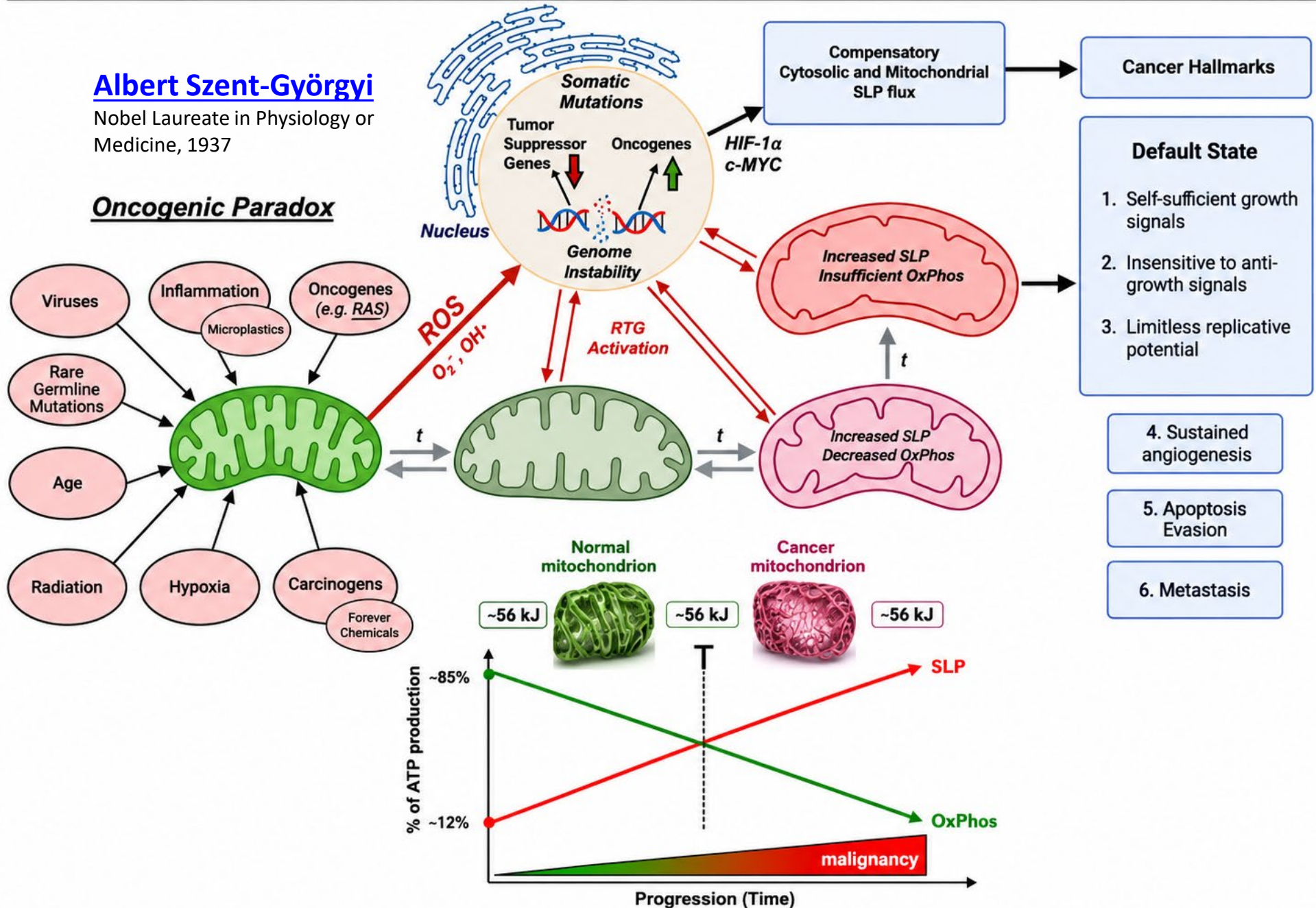
Enzyme / Regulatory Factor (Full Name)	Normal Role	Change in Warburg Effect	Functional Impact
 GLUT1 / GLUTs (Glucose Transporter 1 / Glucose Transporters)	 Transport glucose across the cell membrane	 Upregulated	 Enhances glucose uptake to fuel glycolysis
 HK2 (Hexokinase 2)	 Phosphorylates glucose to glucose-6-phosphate	 Upregulated	 Traps glucose in cells, committing it to glycolysis
 PKM2 (Pyruvate Kinase M2)	 Catalyzes PEP to pyruvate (glycolysis)	 Upregulated	 Less active isoform allows glycolytic intermediate accumulation for biosynthesis
 LDHA (Lactate Dehydrogenase A)	 Converts pyruvate to lactate	 Upregulated	 Regenerates NAD ⁺ to sustain glycolysis and exports lactate to acidify the microenvironment
 PDK (Pyruvate Dehydrogenase Kinase)	 Inhibits pyruvate dehydrogenase (PDH) 	 Upregulated	 Reduces acetyl-CoA entry into TCA cycle, favoring lactate production
 PGAM1 (Phosphoglycerate Mutase 1)	 Converts 3-phosphoglycerate to 2-phosphoglycerate	 Upregulated	 Supports alternative glycolytic flux without ATP generation
 PFK (Phosphofructokinase)	 Rate-limiting enzyme in glycolysis	 Upregulated	 Accelerates glycolytic flux
 HIF-1α (Hypoxia-Inducible Factor 1-alpha)	 Hypoxia-inducible transcription factor	 Upregulated	 Activates glycolytic genes (e.g., GLUT1, LDHA) under low oxygen
 c-Myc (Cellular Myelocytomatosis Oncogene)	 Transcription factor	 Upregulated	 Drives expression of HK2, LDHA, PDK1, and GLUT1
 p53 (Tumor Protein p53)	 Tumor suppressor	 Downregulated	 Loss of function reduces inhibition of glycolysis and promotes TIGAR downregulation

Abbreviations: G6P = Glucose-6-phosphate; PEP = Phosphoenolpyruvate; 3-PG = 3-Phosphoglycerate; 2-PG = 2-Phosphoglycerate; NAD⁺ = Nicotinamide Adenine Dinucleotide (oxidized); PDH = Pyruvate Dehydrogenase; TCA = Tricarboxylic Acid Cycle; ATP = Adenosine Triphosphate; TIGAR = TP53-Induced Glycolysis and Apoptosis Regulator.

Albert Szent-Györgyi

Nobel Laureate in Physiology or Medicine, 1937

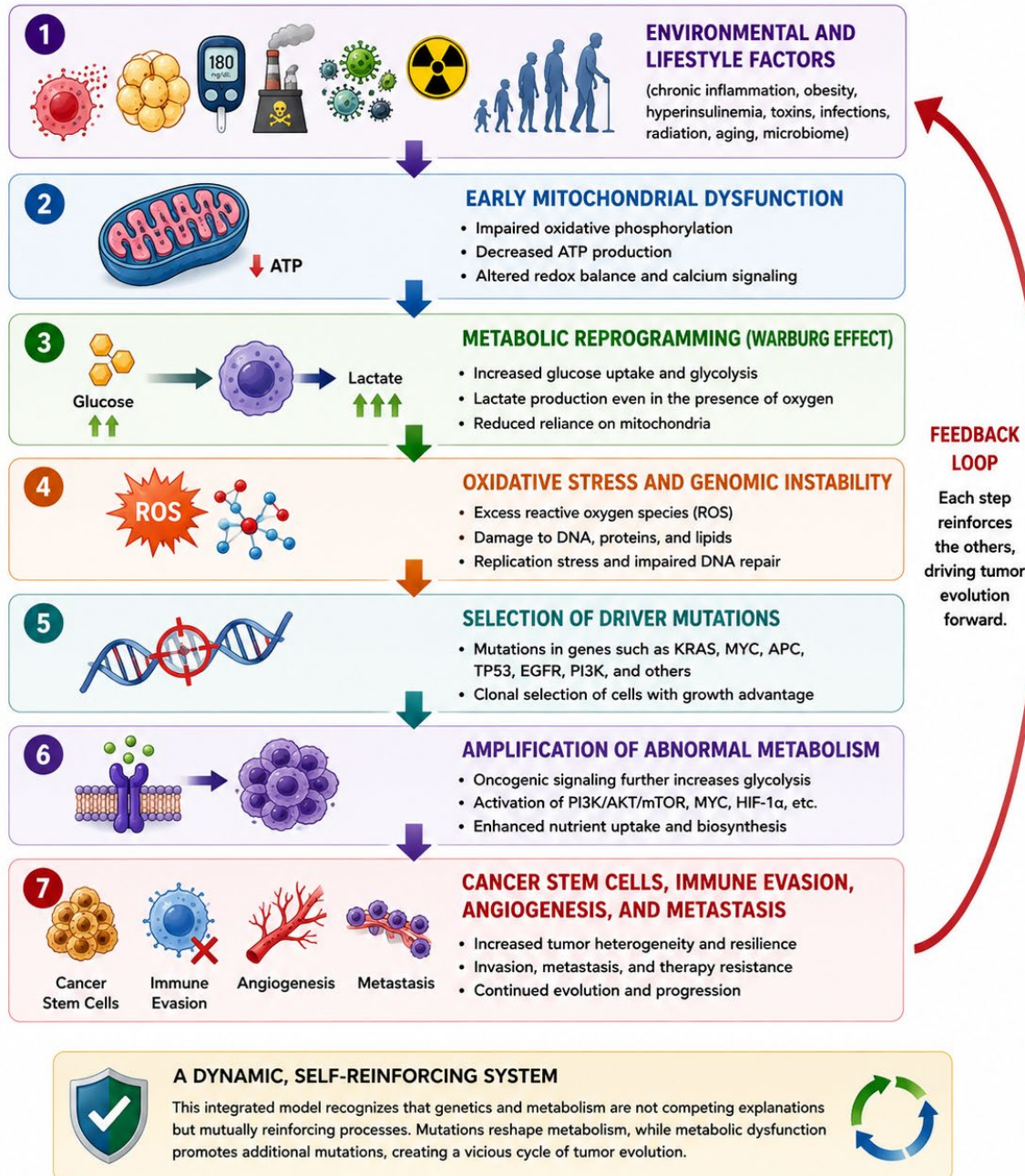
Oncogenic Paradox



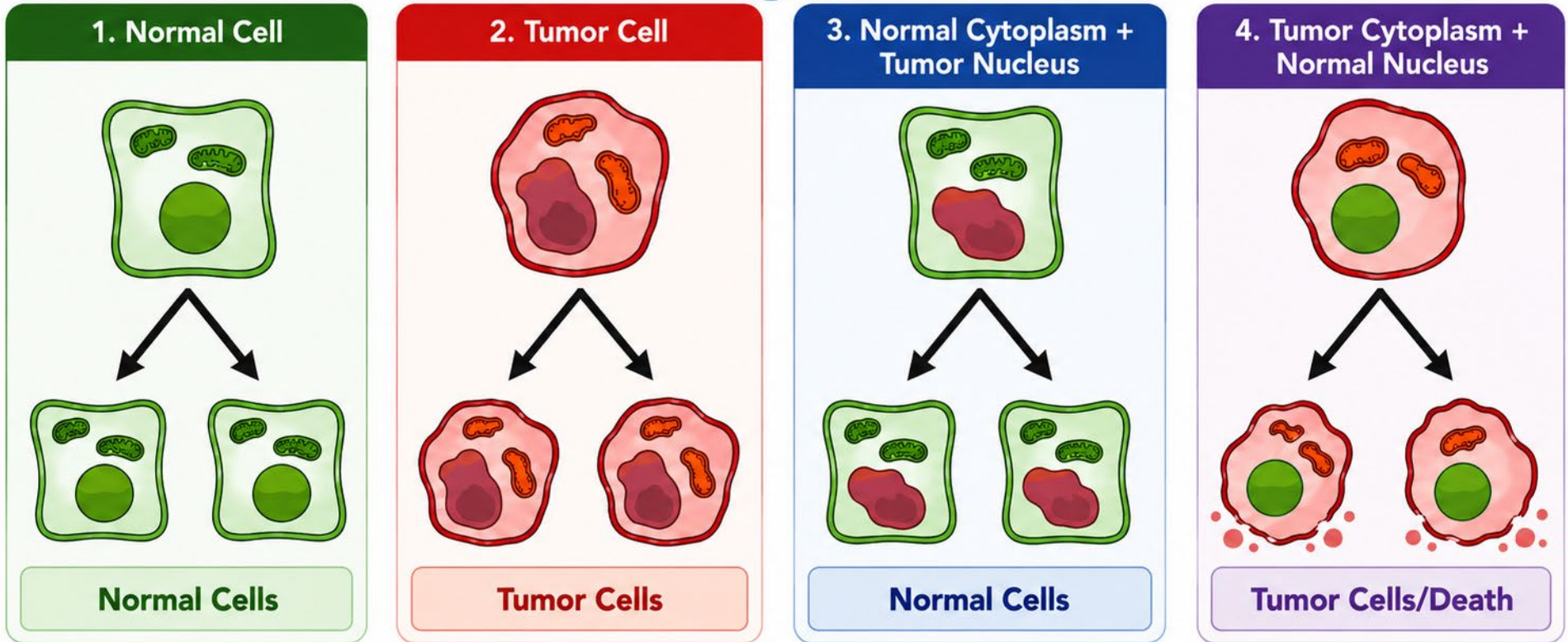
SLP=Substrate level phosphorylation

AN INTEGRATED MODEL OF CANCER

A Systems Biology Framework of Tumor Development and Progression



Role of the Nucleus and Mitochondria in the Origin of Cancer



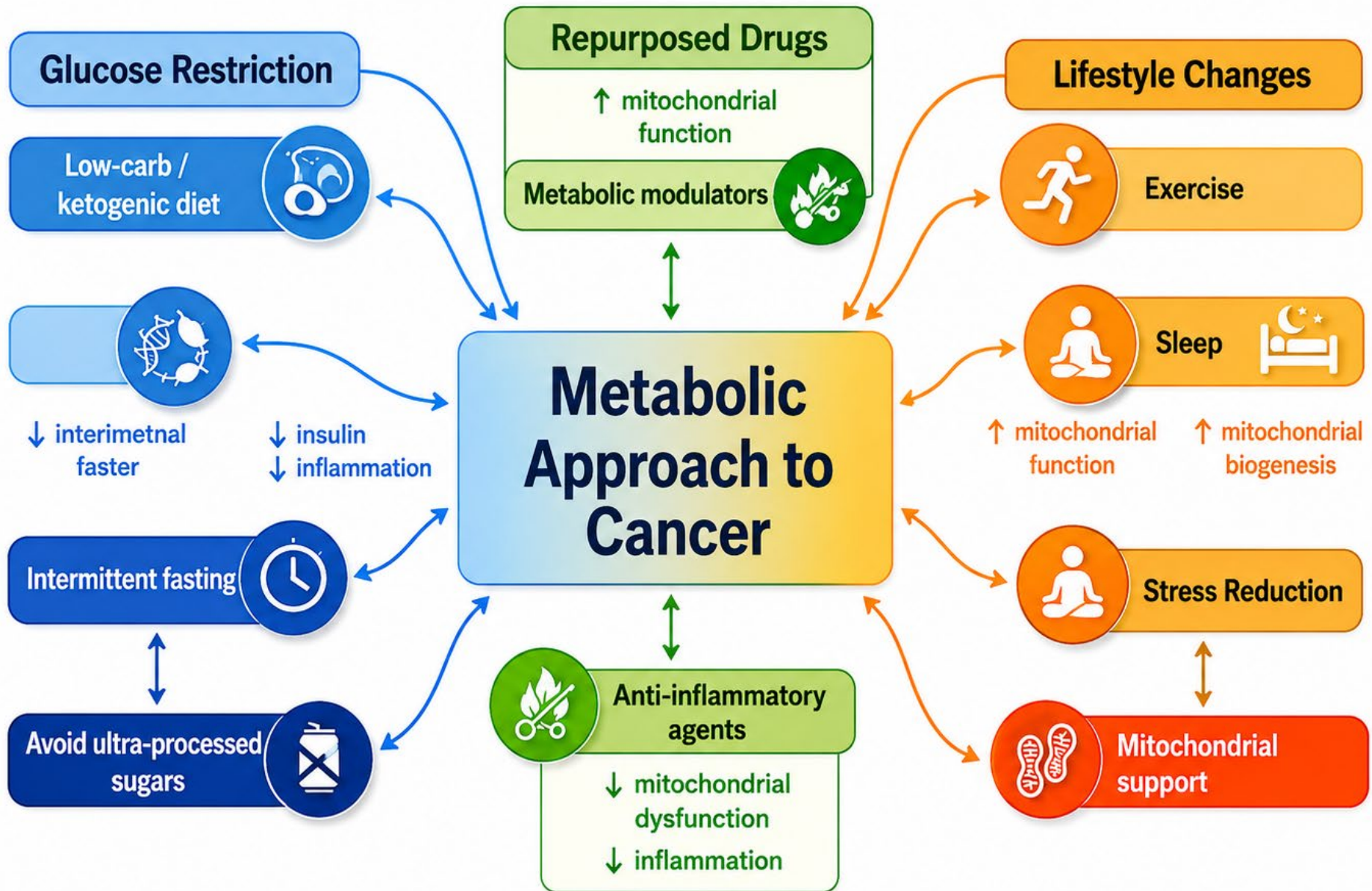
Key Insight: The nucleus contains genetic information that does not transform normal cells into tumor cells.

Mitochondria and cytoplasm from tumor cells can promote tumor behavior and induce stress, dysfunction, and cell death in normal cells.



Seyfried, Cancer as a Metabolic Disease, 2012 John Wiley Press;
Seyfried et al., 2015, Frontiers Cell & Dev. Biol.

Overall Metabolic Approach to Management of Cancer



This integrated metabolic approach aims to improve mitochondrial function, reduce inflammation, support immune function, and limit the metabolic factors that promote cancer growth and progression.

CANCER THERAPY STRATEGIES

LIMITED THERAPY

Diet: Low carbohydrate, low-glycemic diet. Add broccoli sprouts (sulforaphane), matcha tea, brewed green tea (~4 cups/day)

- **Ivermectin:** 0.2–0.4 mg/kg/daily (commonly 0.3 mg/kg/daily)
- **Vitamin D + K2:** Vitamin D 10,000 IU and vitamin K2 100 mcg daily; with monitoring of 25-OH vitamin D and parathyroid hormone (PTH) levels
- **Curcumin:** High-bioavailability extract, 2–4 g daily, titrated up to 8 g/day
- **Doxycycline:** 50 mg daily taken with 2 g oral vitamin C (consider cycling after 6 months)
- **Melatonin:** 20 mg at night, titrated upward from 5 mg
- **Propranolol:** 10–40 mg twice daily as tolerated
- **Green tea extract (EGCG):** Twice daily, less than 800 mg/day
- **Berberine:** 500 mg twice daily
- **Resveratrol:** 500 mg twice daily (high bioavailability)



*Cancer is a complicated disease, and patient care should be supervised by an integrative clinician: **patients should not treat themselves.***

CORE AGENTS



IVERMECTIN



MEBENDAZOLE



DOXYCYCLINE



CURCUMIN

AGGRESSIVE THERAPY

Diet: Low glycemic ketogenic diet, OMAD (one-meal-a-day) and periodic 48 and 72 hour fasting (7 days fast if feasible every other month)

- **Ivermectin:** 0.4–0.8 mg/kg/daily (commonly 0.6 mg/kg/daily)
- **Mebendazole:** 200 mg daily
- **Curcumin:** High-bioavailability extract, 2–4 g daily, titrated up to 8 g/day
- **Vitamin D + K2:** Vitamin D 10,000 IU and vitamin K2 100 mcg daily; with monitoring of 25-OH vitamin D and PTH; titrate to achieve a low-normal PTH level (Coimbra protocol)
- **Green tea extract (EGCG):** Twice daily, less than 800 mg/day
- **Berberine:** 500 mg twice daily
- **Resveratrol:** 500 mg twice daily (high bioavailability)
- **Doxycycline:** 50 mg daily taken with 2 g oral vitamin C
- **Sulforaphane:** Free stabilized sulforaphane from broccoli seed extract (dosage varies)
- **Metformin:** 500–1,000 mg twice daily
- **Propranolol:** 10–40 mg twice daily
- **Melatonin:** 20 mg at night, titrated upward from 5 mg
- **Modified Citrus Pectin (PectaSol):** 14.4 g daily; six capsules, 3x a day
- **Omega-3 fatty acids:** 2–4 g daily
- **Statins:** Atorvastatin 40–80 mg daily or simvastatin 40 mg daily; avoid long-term use or precipitous LDL reduction, which may increase dementia risk
- **Quercetin:** 500–1,000 mg twice daily
- **Alpha lipoic acid:** 300–600 mg daily
- **Dandelion extract:** 250–1,000 mg twice daily
- **Methylene blue:** 10–50 mg daily
- **Artesunate:** 200 mg daily
- **Low-dose naltrexone:** 2–4.5 mg daily
- **Epigepin (apigenin):** 50–400 mg/day
- **Pomegranate extract:** 250 mg daily
- **Aged garlic extract:** 1,000 mg daily
- **Monk fruit extract:** As sweetener



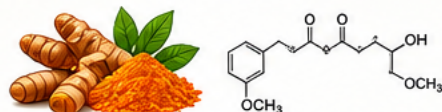
**CANCER IS BEST VIEWED AS A COMPLEX ADAPTIVE SYSTEM DISEASE—
NOT PURELY A GENETIC DISEASE.**

TOP UNIVERSAL ANTI-CANCER AGENTS

Broad-Spectrum • Multi-Target • Works Across Many Cancer Types

Targeting Multiple Hallmarks of Cancer Through Different Mechanisms

1 CURCUMIN



Powerful anti-inflammatory & multi-target agent

- ✓ Inhibits NF-κB, STAT3, COX-2
- ✓ Suppresses growth, angiogenesis & metastasis
- ✓ Induces apoptosis & cell-cycle arrest
- ✓ Targets cancer stem cells
- ✓ Enhances immune response

Key Pathways: NF-κB, STAT3, Wnt, PI3K/AKT/mTOR, Nrf2, COX-2

2 EGCG

(from Green Tea)

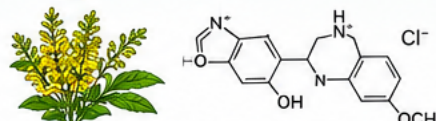


Potent antioxidant & signaling modulator

- ✓ Inhibits EGFR, VEGF, Wnt/β-catenin
- ✓ Induces apoptosis & inhibits proliferation
- ✓ Targets cancer stem cells
- ✓ Anti-angiogenic & anti-metastatic
- ✓ Enhances immune function

Key Pathways: EGFR, Wnt/β-catenin, PI3K/AKT, MAPK, NF-κB

3 BERBERINE

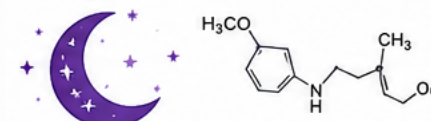


Metabolic master regulator

- ✓ Activates AMPK, inhibits PI3K/AKT/mTOR
- ✓ Suppresses glycolysis (Warburg effect)
- ✓ Induces apoptosis & cell-cycle arrest
- ✓ Anti-inflammatory & anti-angiogenic
- ✓ Targets cancer stem cells

Key Pathways: AMPK, PI3K/AKT/mTOR, NF-κB, STAT3, HIF-1α, Wnt

4 MELATONIN

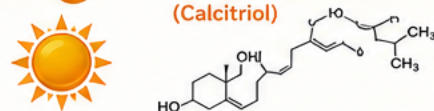


Hormone of darkness & immune support

- ✓ Antioxidant & reduces oxidative stress
- ✓ Induces apoptosis & inhibits proliferation
- ✓ Regulates circadian rhythm & DNA repair
- ✓ Enhances immune surveillance
- ✓ Anti-angiogenic

Key Pathways: MT1/MT2, NF-κB, STAT3, HIF-1α, p53

5 VITAMIN D (Calcitriol)

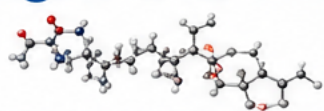


Hormone with broad anti-cancer effects

- ✓ Induces differentiation & growth inhibition
- ✓ Modulates immune response
- ✓ Inhibits angiogenesis & metastasis
- ✓ Enhances apoptosis
- ✓ Reduces inflammation

Key Pathways: VDR, Wnt/β-catenin, NF-κB, PI3K/AKT, p53

6 IVERMECTIN

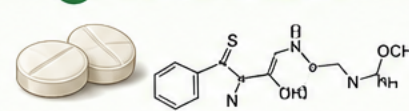


Anti-parasitic with anti-cancer activity

- ✓ Inhibits Wnt/β-catenin signaling
- ✓ Induces apoptosis & autophagy
- ✓ Targets cancer stem cells
- ✓ Anti-proliferative & anti-metastatic
- ✓ Synergizes with other agents

Key Pathways: Wnt/β-catenin, P-gp, NF-κB, PI3K/AKT

7 MEBENDAZOLE



Anti-helminthic with multi-target actions

- ✓ Disrupts microtubules (mitotic arrest)
- ✓ Inhibits angiogenesis (↓ VEGF)
- ✓ Targets cancer stem cells
- ✓ Inhibits Wnt, Hedgehog & BRAF (mut)
- ✓ Induces apoptosis

Key Pathways: β-tubulin, Wnt, Hedgehog, VEGF, BRAF, PI3K/AKT

8 DOXYCYCLINE



Antibiotic with anti-cancer properties

- ✓ Inhibits mitochondrial protein synthesis
- ✓ Targets cancer stem cells
- ✓ Inhibits MMPs, EMT & metastasis
- ✓ Anti-inflammatory & anti-angiogenic
- ✓ Enhances sensitivity to therapies

Key Pathways: MMPs, NF-κB, EMT, STAT3, Mitochondrial function

WHY THESE AGENTS?



Multi-Target
Hit many pathways at once



Broad-Spectrum
Active across many cancer types



Low Toxicity
Generally well tolerated



Synergistic
Work better together

THE 5-AXIS METABOLIC TRAP



METABOLISM
(Glycolysis, Insulin/mTOR)



MITOCHONDRIA / CANCER STEM CELLS
(Energy, Survival)



CELL DIVISION / CYTOSKELETON
(Proliferation)



TUMOR MICRO-ENVIRONMENT
(Inflammation, Angiogenesis)



IMMUNE RESTORATION
(Immune Balance)

These 8 agents collectively target all 5 axes for maximal anti-cancer effect.

IMPORTANT NOTE



Extensive preclinical evidence supports the anti-cancer activity of these agents.



Clinical evidence is evolving. These agents are not approved as cancer treatments.



Always consult your healthcare professional before starting any therapy.



SIMPLE. SAFE. MULTITARGET. UNIVERSAL. A POWERFUL FOUNDATION FOR INTEGRATIVE CANCER CARE.

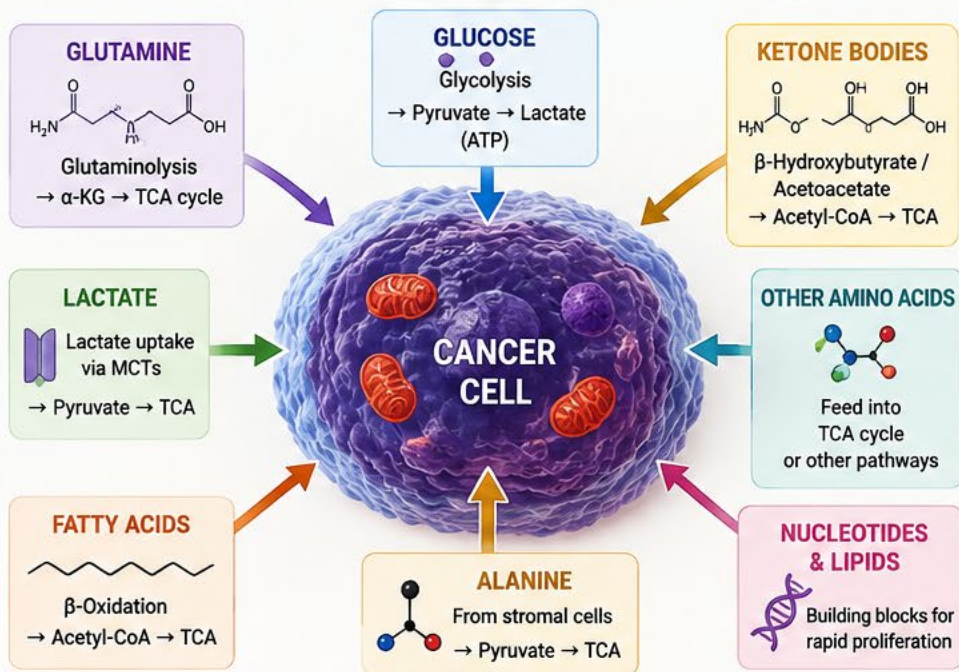


CANCER CELLS ARE METABOLICALLY FLEXIBLE

Block one pathway... cancer finds another.

MULTIPLE FUELS. MULTIPLE PATHWAYS.

Cancer cells can tap many energy sources to survive and grow.



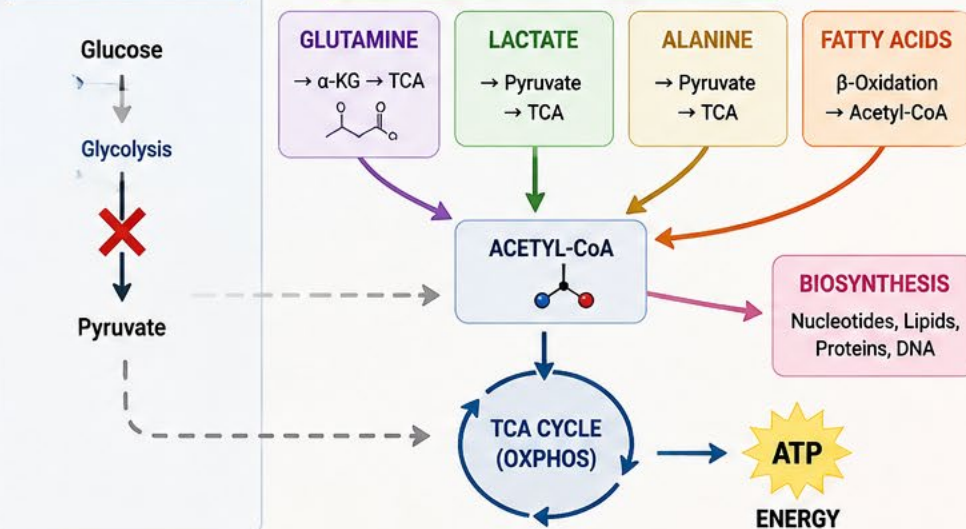
This metabolic diversity allows cancer cells to adapt, survive stress, and resist therapy.

BLOCK ONE PATHWAY... CANCER TAKES A DETOUR.

When a single pathway is inhibited, cancer cells reroute through alternative fuels and pathways to keep growing.

1. BLOCK GLYCOLYSIS

2. COMPENSATORY ROUTES ACTIVATE



Block one road, and cancer cells open another.
This is why single-target therapies often fail and resistance develops.

THE SOLUTION: HIT CANCER WHERE IT HURTS – EVERYWHERE



Multi-targeted strategies limit escape routes and reduce metabolic flexibility.

- ✓ Block multiple fuels
- ✓ Inhibit key metabolic nodes
- ✓ Target the tumor microenvironment
- ✓ Disrupt survival and stress pathways



Comprehensive metabolic pressure leaves cancer cells no way out.

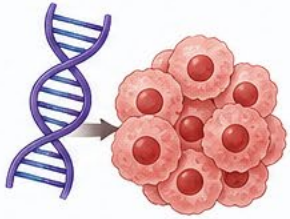
COMBINATION & METABOLIC STRATEGIES CREATE SUSTAINED CONTROL AND BETTER OUTCOMES

CANCER IS RARELY SUSTAINED BY A SINGLE ABNORMAL PATHWAY

A tumor may begin with a dominant genetic alteration, but established cancers develop a network of adaptations that allow them to survive therapy and recur.

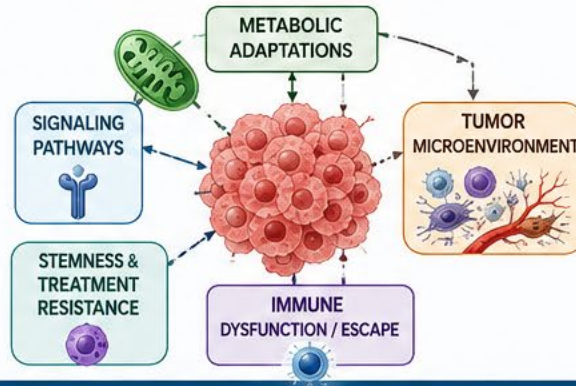
1. INITIATING ALTERATION

A dominant genetic change may initiate tumor growth.



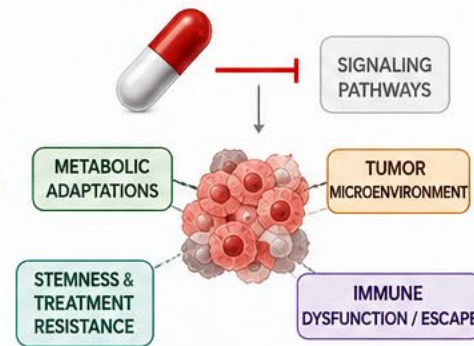
2. BIOLOGICAL NETWORK

The tumor develops multiple, interconnected adaptations across key systems.



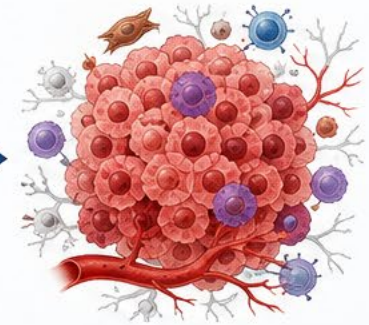
3. THERAPY TARGETS ONE PATHWAY

Inhibiting a single pathway may shrink the tumor initially.



4. ADAPTATION & RECURRENCE

Parallel systems compensate, allowing survival, regrowth and recurrence.



Inhibiting one pathway can produce a dramatic initial response — but the tumor's network of adaptations enables escape and recurrence.

A MULTI-AXIS STRATEGY: SIMULTANEOUS PRESSURE ON MULTIPLE SYSTEMS

Instead of looking for a single Achilles' heel, a multi-axis approach targets the five interrelated hallmarks that cancer depends on for survival.

1. METABOLIC DEPENDENCE

Cancer cells rely on specific metabolic fuels and pathways.



- Glycolysis
- Glutaminolysis
- Lipid metabolism
- Mitochondrial function

2. METABOLIC FLEXIBILITY

Cancer adapts by switching fuels and pathways when one route is blocked.



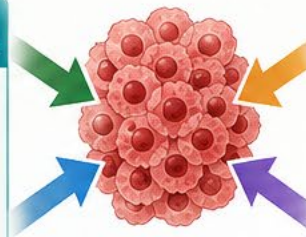
- Alternative energy sources
- Pathway plasticity
- Stress adaptation

3. STEMNESS & TREATMENT RESISTANCE

Cancer stem-like cells drive relapse and resist therapy.



- Self-renewal
- Drug resistance
- Quiescence
- DNA repair



**COMBINED PRESSURE
REDUCES ADAPTATION,
RESISTANCE AND
RECURRENCE**

4. TUMOR MICROENVIRONMENT

The microenvironment provides support, protection and resources.



- Stromal support
- Angiogenesis
- Hypoxia
- Inflammation

5. IMMUNE DYSFUNCTION OR ESCAPE

Cancer evades immune surveillance and suppresses anti-tumor immunity.



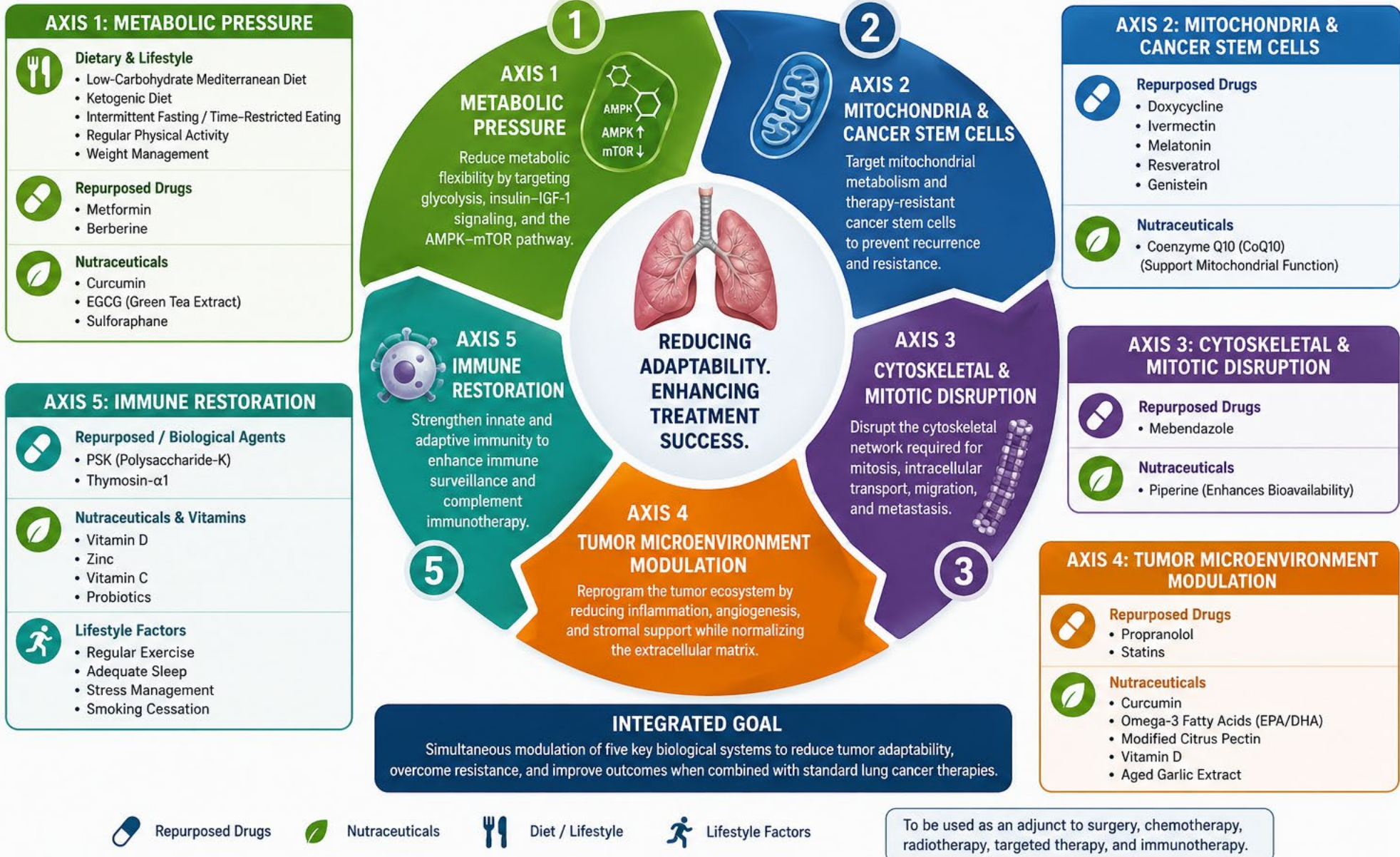
- Immune checkpoints
- Immunosuppressive cells
- Antigen loss
- Cytokine dysregulation



By attacking multiple, interdependent systems at once, a multi-axis strategy aims to collapse the tumor's ability to adapt, improve durability of response, and reduce the risk of recurrence.

The Five-Axis Metabolic Trap

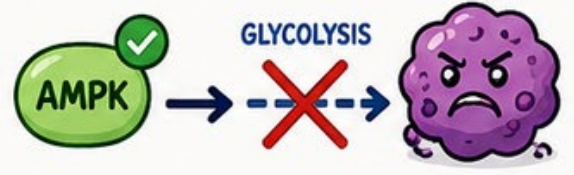
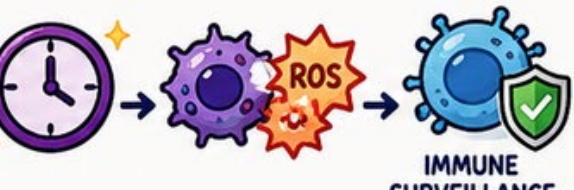
A Systems Biology Framework to Complement Precision Oncology in Lung Cancer





The Real Metabolic "Trap"

Multi-axis metabolic pressure in cancer

Targeted energy system	Therapeutic agents	Mechanistic effect on tumor cells
 Glucose metabolism	Metformin, Berberine	Activates AMPK, reduces insulin signaling, suppresses glycolysis and tumor growth signaling 
 Mitochondrial function	Doxycycline	Inhibits mitochondrial ribosomes and oxidative phosphorylation, targeting cancer stem cell metabolism 
 Cytoskeleton / mitosis	Mebendazole	Disrupts β -tubulin polymerization and mitotic spindle formation 
 Adrenergic signaling	Propranolol	Reduces β -adrenergic signaling, angiogenesis, and stress-mediated tumor progression 
 Circadian / oxidative stress regulation	Melatonin	Enhances circadian control, increases oxidative stress in tumor cells, supports immune surveillance 

Proposed Suitability of Different Cancers for a Five-Axis Adjunctive Strategy

Based on Five Biological Characteristics That Drive Tumor Persistence, Resistance & Recurrence

TIER 1 STRONGEST BIOLOGICAL RATIONALE

Strong expression of
all five biological
characteristics

These cancers show extensive metabolic reprogramming, stemness, TME support, immune escape, and metabolic plasticity.

- Glioblastoma / high-grade glioma
- Pancreatic adenocarcinoma
- Triple-negative breast cancer
- Colorectal cancer
- KRAS-mutant NSCLC
- Ovarian cancer
- Metastatic / castration-resistant prostate cancer
- Melanoma
- Clear-cell renal-cell carcinoma
- Hepatocellular carcinoma



TIER 2 STRONG RATIONALE, LESS CLINICAL/ TRANSLATIONAL SUPPORT

Many Five-Axis
features present,
but evidence for
adjunctive benefit
is less developed

Substantial Five-Axis biology, often heterogeneous disease or limited clinical data for adjunctive interventions.

- Endometrial cancer
- ER-positive breast cancer
- HER2-positive breast cancer
- Bladder / urothelial carcinoma
- Head & neck squamous-cell carcinoma
- Gastric adenocarcinoma
- Esophageal adenocarcinoma
- Esophageal squamous-cell carcinoma
- Cholangiocarcinoma
- Cervical cancer
- Small-cell lung cancer
- Mesothelioma
- Thyroid cancer, advanced / dedifferentiated
- Adrenocortical carcinoma
- Selected soft-tissue sarcomas
- Osteosarcoma
- Chordoma



TIER 3 BIOLOGICALLY PLAUSIBLE, HIGHLY CONTEXT- DEPENDENT

Important biology,
but disease or
treatment context
limits priority for
aggressive adjunctive
pharmacology

Relevance of the Five Axes varies by subtype and patient.
Emphasize supportive metabolic health and safety.

- Follicular lymphoma
- Mantle-cell lymphoma
- CLL / SLL
- Multiple myeloma
- AML (acute myeloid leukemia)
- MDS (myelodysplastic syndromes)
- ALL (acute lymphoblastic leukemia)
- Neuroendocrine tumors
- Low-grade glioma
- GIST (gastrointestinal stromal tumor)
- Germline-associated tumors with effective targeted strategies
- Other select sarcomas
- Rarer malignancies with limited data or highly variable biology



TIER 4 LOW PRIORITY FOR EXPERIMENTAL FIVE-AXIS DRUG THERAPY

Very high cure rates
or excellent outcomes
with established
therapy—risk/benefit
unfavorable for
unproven adjuncts

Standard therapy already has high probability of cure.

- Diffuse large B-cell lymphoma (DLBCL)
- Testicular germ-cell cancer
- Classical Hodgkin lymphoma
- Early-stage favorable breast cancer
- Differentiated thyroid cancer
- Early-stage melanoma
- Basal-cell carcinoma
- Cutaneous squamous-cell carcinoma
- Early-stage cervical cancer
- Many pediatric leukemias
- Wilms tumor
- Retinoblastoma
- Other highly curable cancers with established regimens



Tumors that strongly express ALL FIVE characteristics (Tier 1) have the strongest biological rationale for a multi-axis adjunctive strategy.



This framework is intended to guide hypothesis generation and research prioritization—not to replace judgment or individualized clinical decision-making.



Evidence for most adjunctive metabolic strategies remains preclinical or early clinical. Safety, interactions, and treatment context are critical.

THE FIVE AXES of Tumor Persistence



1. METABOLIC DEPENDENCE

Reliance on altered energy and biosynthetic pathways: glycolysis, glutaminolysis, OXPHOS, lipid metabolism, insulin/IGF signaling.



2. METABOLIC FLEXIBILITY

Ability to switch fuels and energy pathways to escape single-pathway blockade.



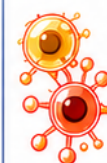
3. STEMNESS & TREATMENT RESISTANCE

Cancer stem-like cells, EMT programs, drug-tolerant persister cells, anti-apoptotic signaling, and drivers of recurrence.



4. TUMOR MICROENVIRONMENT

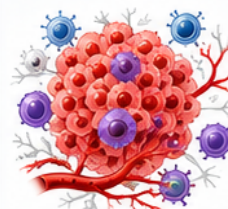
Supportive microenvironment with hypoxia, chronic inflammation, angiogenesis, fibrosis, abnormal stromal signaling, and nutrient competition.



5. IMMUNE DYSFUNCTION & ESCAPE

Immune suppression and evasion via checkpoint signaling, suppressive cells and cytokines, impaired surveillance, and metabolic competition with immune cells.

OUTCOME WHEN AXES ARE ACTIVE:



PERSISTENCE RESISTANCE RECURRENCE



Simultaneous pressure on
multiple systems reduces
the tumor's ability to adapt,
improves durability of
response, and reduces
recurrence risk.

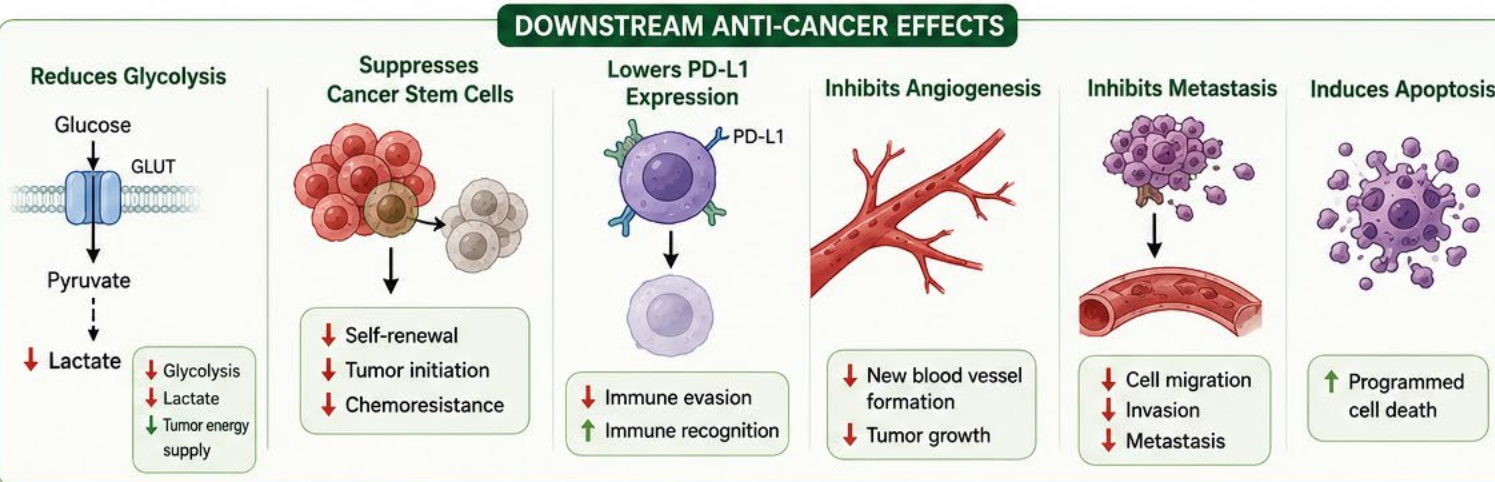
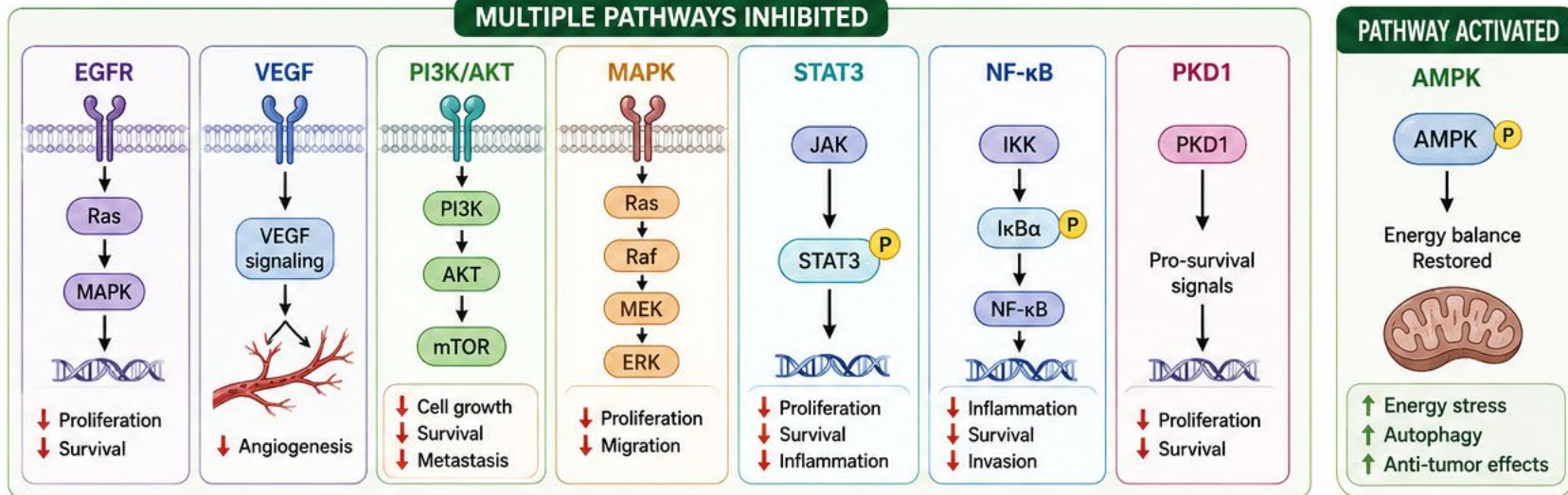
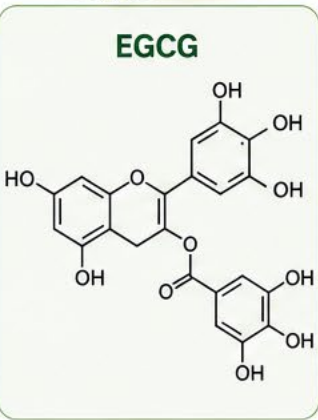
BIOLOGICAL FRAMEWORK—NOT A VALIDATED CLINICAL RESPONSE RANKING.

The Five-Axis Adjunctive Approach is a hypothesis-generating model. Clinical outcomes depend on many factors, including molecular subtype, performance status, standard therapy, and individual patient biology.

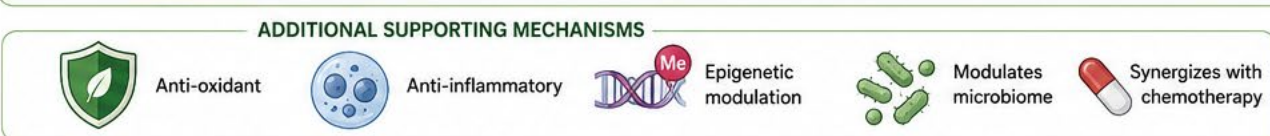


EGCG (Epigallocatechin-3-gallate): Multi-Targeted Anti-Cancer Activity

EGCG, the most abundant catechin in green tea, acts on multiple signaling pathways to inhibit tumor growth, metastasis and immune evasion while activating cellular energy regulation.



- SUMMARY**
- ✓ Inhibits 7 major oncogenic pathways: EGFR, VEGF, PI3K/AKT, MAPK, STAT3, NF-κB, PKD1
 - ✓ Activates AMPK to restore energy balance
 - ✓ Reduces glycolysis and lactate production
 - ✓ Suppresses cancer stem cells and chemoresistance
 - ✓ Lowers PD-L1 and enhances immune recognition
 - ✓ Inhibits angiogenesis, metastasis and promotes apoptosis

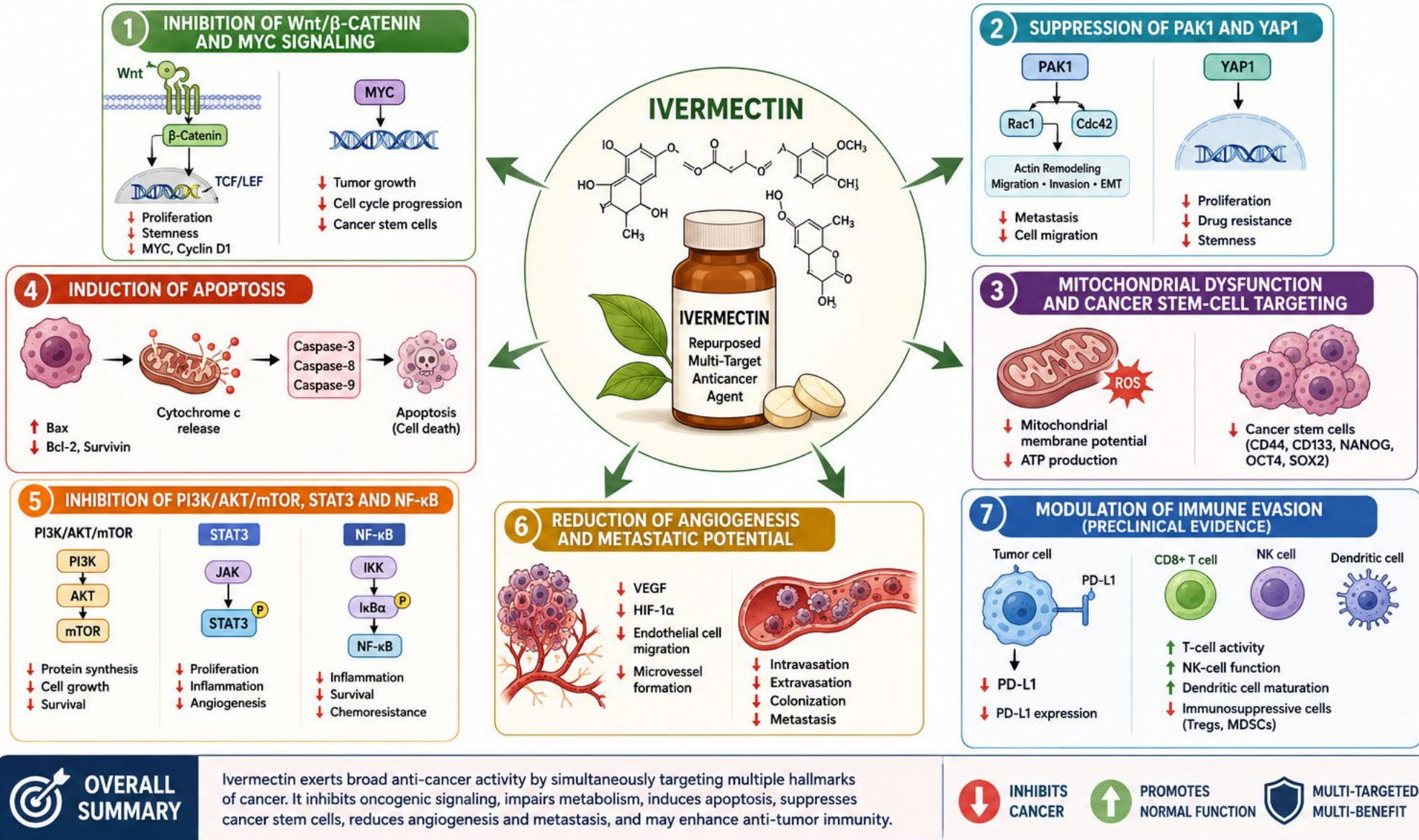


KEY

- ↓ Decrease / Inhibition
- ↑ Increase / Activation

IVERMECTIN: A MULTI-TARGETED ANTI-CANCER AGENT

Acts on Multiple Pathways Simultaneously Rather Than a Single Molecular Target



! IMPORTANT: Most data are preclinical (in vitro and animal studies). Clinical evidence in humans is limited. Ivermectin is not approved as a cancer treatment.

Repurposed Drugs and Nutraceuticals Mapped to the 5-Axis Metabolic Model

AGENT	 GLYCOLYSIS / WARBURG	 MITOCHONDRIA / CSC	 LIPID / MEVALONATE	 CYTOSKELETON / STRUCTURE	 STRESS SIGNALING / MICROENVIRONMENT
 Metformin	Strong	Strong	Mild	—	Moderate
 Berberine	Strong	Strong	Mild	—	Moderate
 Ivermectin	Strong	Moderate	Mild	Mild	Strong
 Atorvastatin	Moderate	Mild	Strong	Mild	Moderate
 Curcumin	Moderate	Moderate	Mild	Mild	Strong
 EGCG	Moderate	Moderate	Mild	—	Moderate
 Resveratrol	Moderate	Moderate	Mild	—	Moderate
 Quercetin	Moderate	Mild	Mild	Mild	Moderate
 Sulforaphane	Moderate	Moderate	Mild	—	Moderate
 Aspirin	Moderate	Mild	Mild	—	Moderate
 Doxycycline	Mild	Strong	—	—	Mild
 Mebendazole	Mild	Mild	—	Strong	Mild
 Omega-3 fatty acids	Mild	Mild	Moderate	Mild	Moderate
 Vitamin D	Mild	Mild	Mild	—	Moderate
 Melatonin	Mild	Moderate	—	—	Moderate
 Propranolol	Mild	—	Mild	—	Strong

Strong
 Strong evidence or primary mechanism of action

Moderate
 Moderate evidence or secondary mechanism

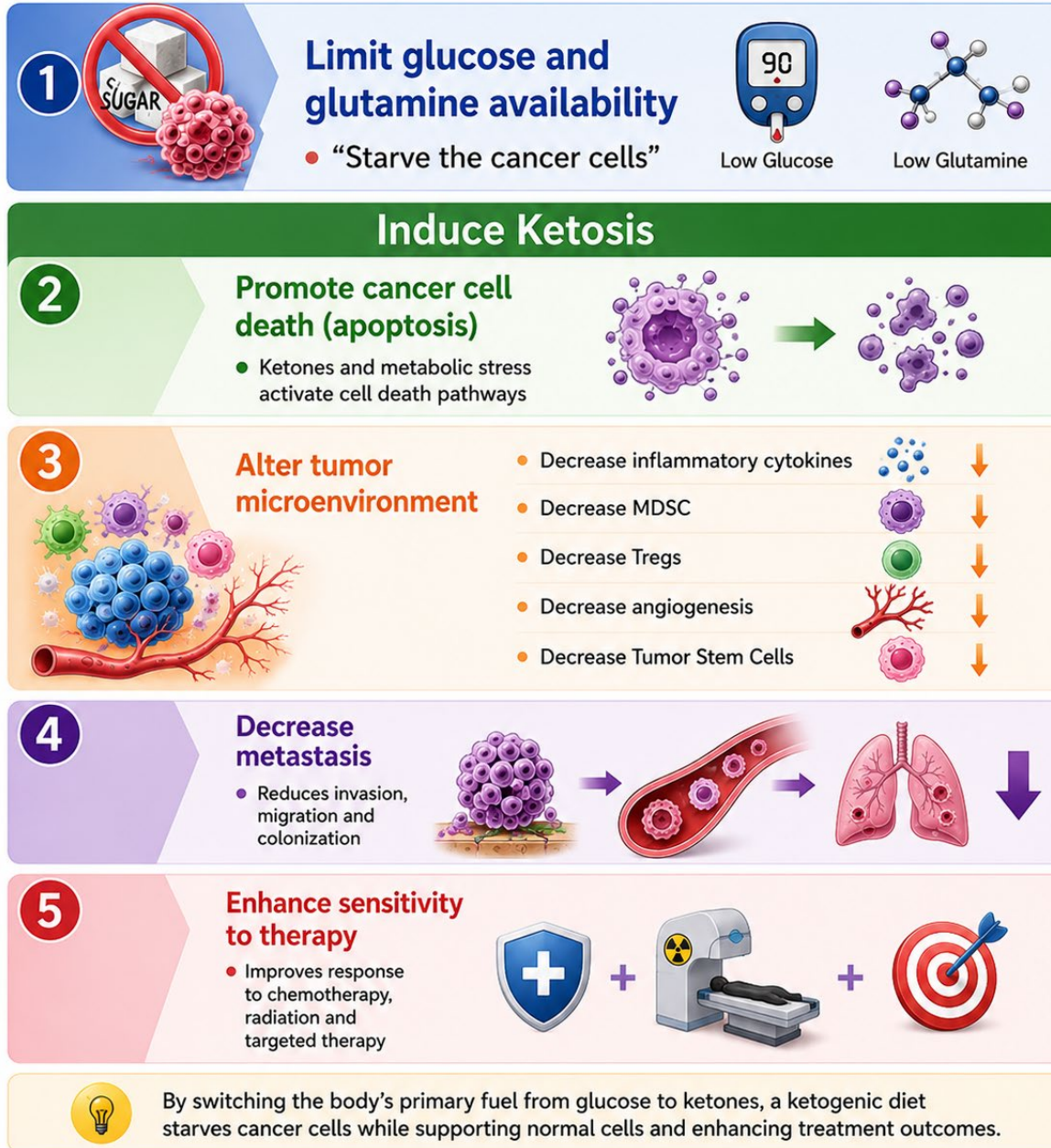
Mild
 Mild evidence or potential effect

—
 No significant evidence or not a primary target

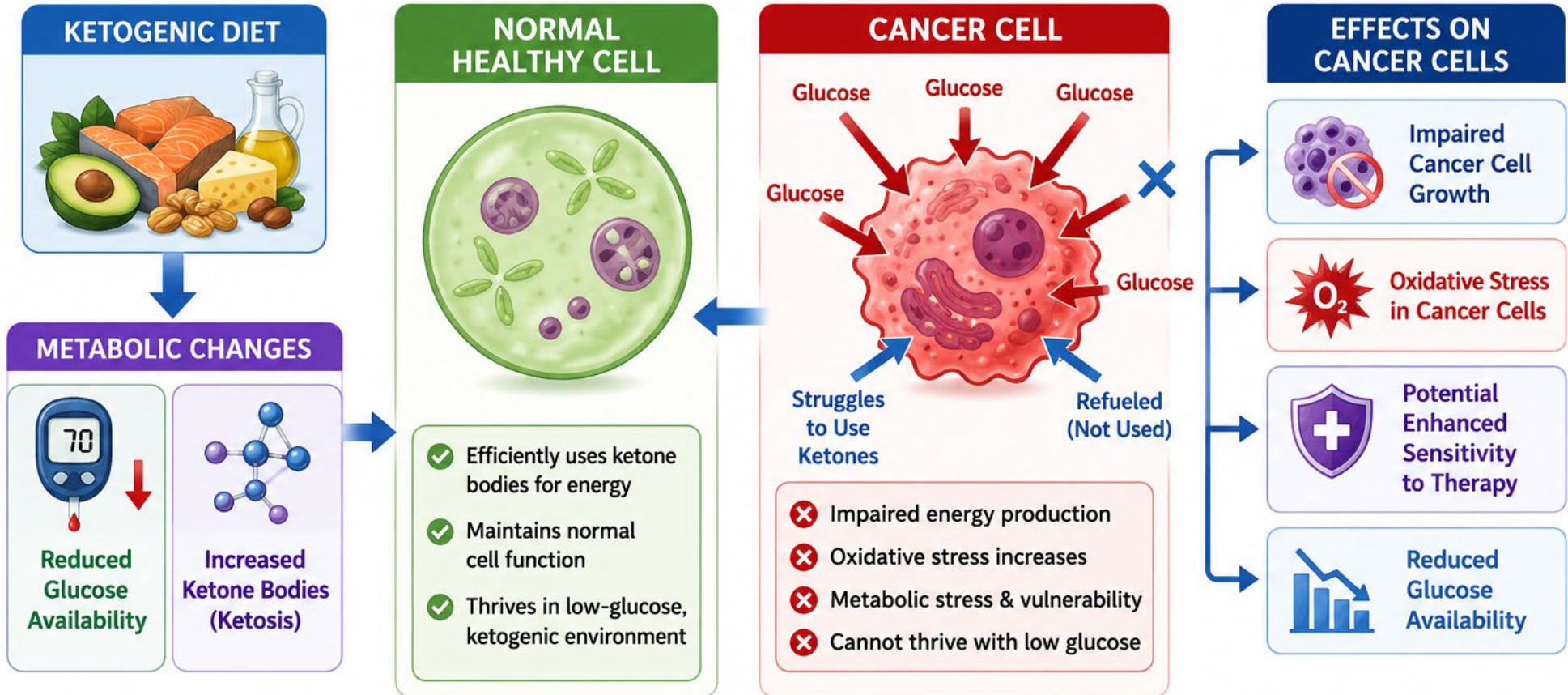


American Society of Clinical Oncology (ASCO) has a formal guideline addressing dietary interventions during active cancer treatment, but it does not specifically recommend a low-glycemic diet.

Metabolic Interventions to Control Cancer



The Effect of a Ketogenic Diet on Normal and Cancer Cells



There are no known drugs that can simultaneously target as many tumor-associated signaling pathways as can calorie restriction.

Glucose Management and Colon Cancer Outcomes

High Dietary Insulin Load Increases the Risk of Recurrence and Mortality

THE STUDY



CALGB 89803
(Alliance)



Stage III
Colon Cancer

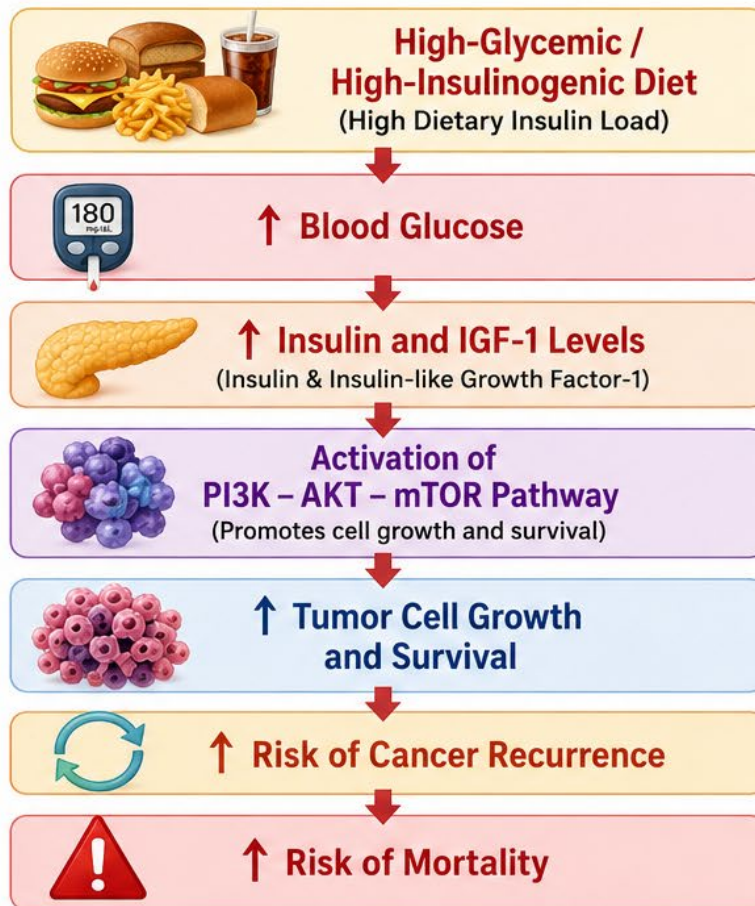


Prospective
Cohort Study



Patients with
resected stage III
colon cancer

Published in:
JNCI J Natl Cancer Inst
(2019) 111(2): djy098



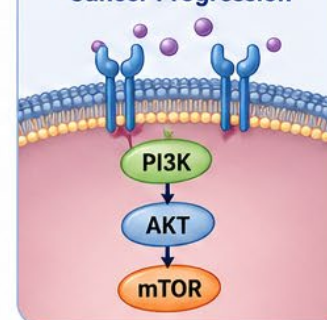
KEY CONCLUSION

Patients with resected stage III colon cancer who consumed a **HIGH-INSULINOGENIC DIET** were at

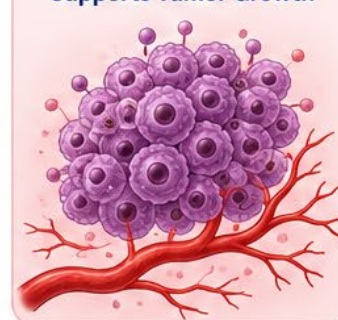
↑ INCREASED RISK of RECURRENCE

↑ INCREASED RISK of MORTALITY

High Insulin Promotes
Cancer Progression



High Insulin Environment
Supports Tumor Growth



CLINICAL IMPLICATION:

Managing glucose and limiting dietary insulin load may be a critical strategy to improve outcomes in colon cancer survivors.



Low-Glycemic
Diet



Regular
Exercise

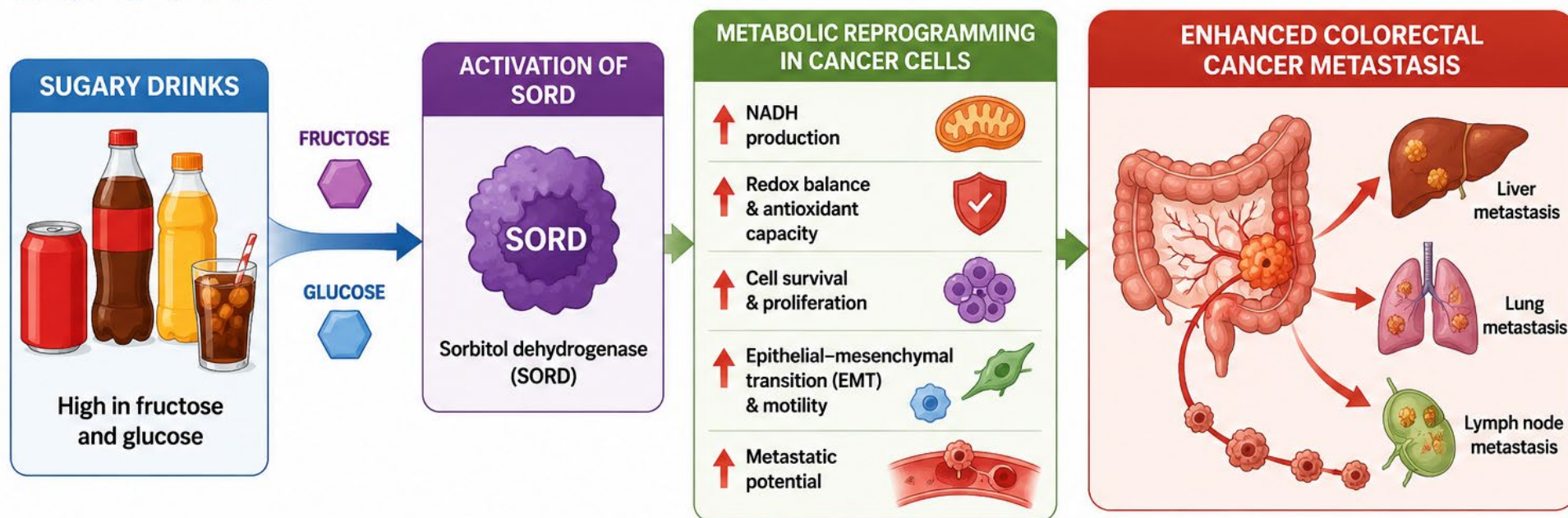


Monitor
Glucose



Lower Insulin
Load

Fructose and glucose from sugary drinks enhance colorectal cancer metastasis via SORD



DIET MATTERS: High intake of sugary drinks (fructose and glucose) activates SORD in colorectal cancer cells, driving metabolic reprogramming that promotes metastasis.

Reducing sugary drink consumption may help limit colorectal cancer spread.

THE FUTURE IS PROBABLY COMBINATION BIOLOGY

Cancer is Complex. A Single Target Is Rarely Enough.

It is unlikely that the future of oncology lies in:



Single-Target Approaches

- One mutation
 - One pathway
 - One drug
-
- ✗ Limited durability
 - ✗ Resistance emerges
 - ✗ Tumor adapts

Rather, the most effective strategies may integrate:



GENOMIC TARGETING

- Target actionable mutations
- Precision informed by genomics



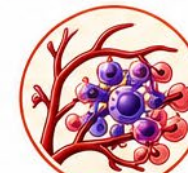
METABOLIC TARGETING

- Disrupt cancer energy pathways
- Block metabolic flexibility
- Starve the tumor



IMMUNE MODULATION

- Reinforce immune recognition
- Overcome immune evasion
- Activate durable anti-tumor immunity



MICROENVIRONMENT REPROGRAMMING

- Normalize vasculature
- Reduce inflammation
- Modify stroma
- Improve drug delivery



STEM-CELL SUPPRESSION

- Target cancer stem cells
- Prevent recurrence
- Reduce metastasis
- Overcome resistance

WHY COMBINATION BIOLOGY?



MULTIPLE HALLMARKS

Hit cancer on several fronts at once.



PREVENT RESISTANCE

Block escape routes and adaptive changes.



DEEPER AND DURABLE RESPONSES

Greater likelihood of meaningful, lasting outcomes.



PATIENT-CENTERED STRATEGIES

Tailor combinations to the biology of each patient.



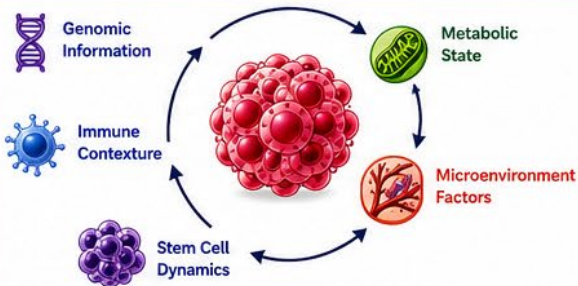
IMPROVED OUTCOMES

Better survival, quality of life, and long-term control.

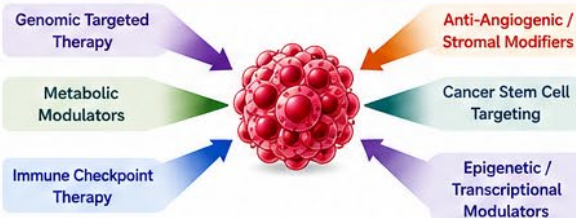
"The goal is not just to treat the cancer, but to outsmart it."



A HOLISTIC, SYSTEMS-BASED APPROACH



EXAMPLE INTEGRATIVE STRATEGY



Different drugs. Different mechanisms.
One coordinated strategy.

THE TAKE-HOME MESSAGE

The future of oncology is not one drug, one target, or one pathway—
it is **combination biology**.



Integrating genomics, metabolism, immunity, the microenvironment, and stem cell biology offers the best chance to transform cancer from a fatal disease to a manageable one.



COMBINATION. COMPLEMENTATION. COORDINATION.

THIS IS WHERE THE FUTURE LIES.





