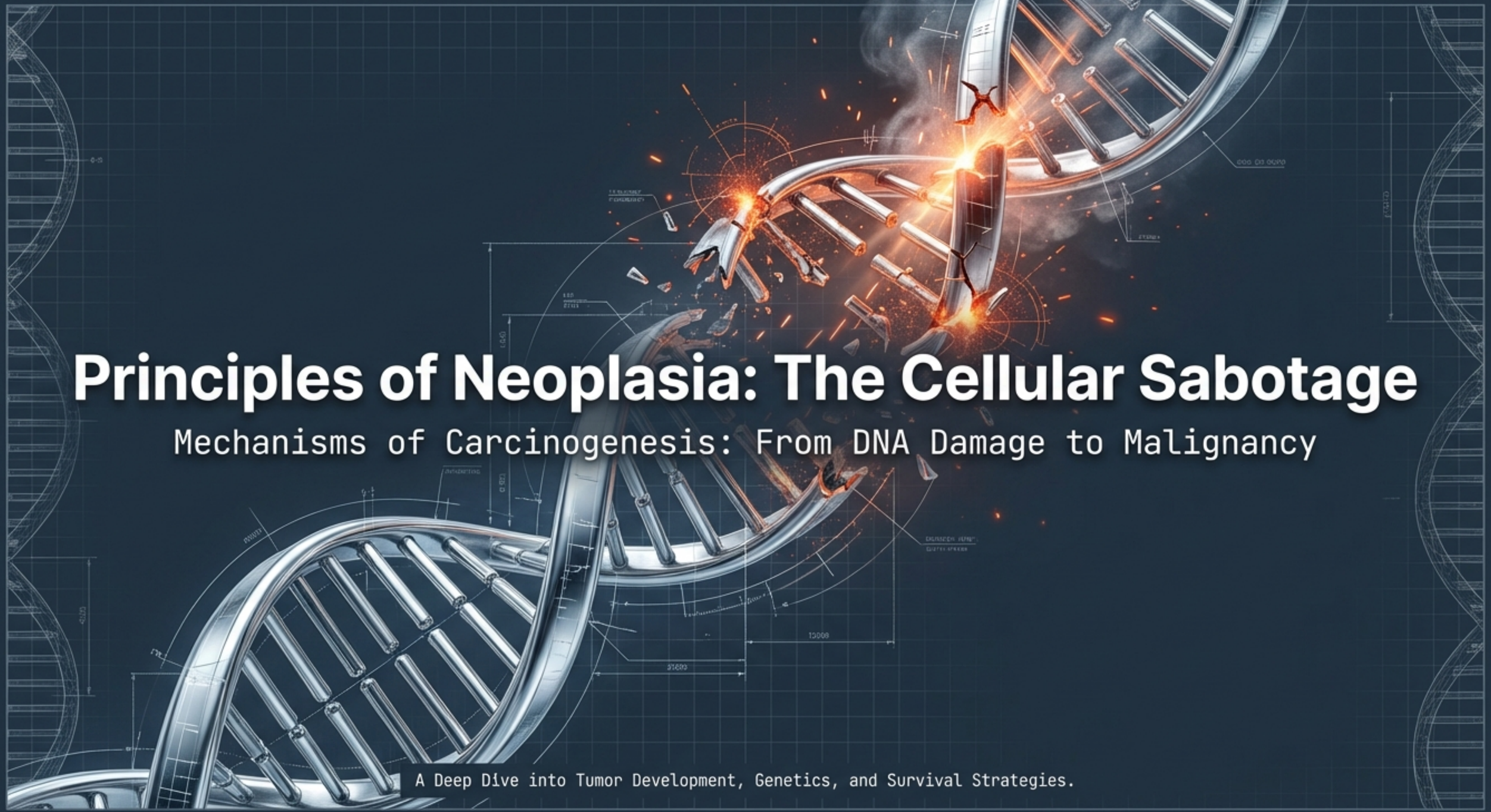


Principles of Neoplasia: The Cellular Sabotage

Mechanisms of Carcinogenesis: From DNA Damage to Malignancy

A Deep Dive into Tumor Development, Genetics, and Survival Strategies.

THE BLUEPRINT OF CHAOS

The Progression from Damage to Metastasis

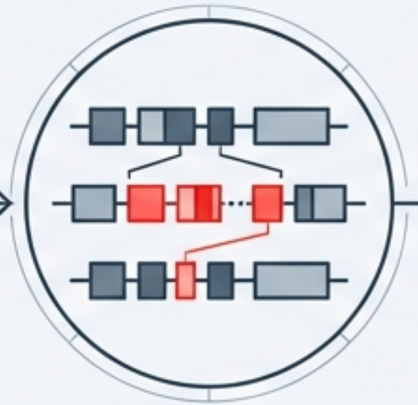
INITIATION

Non-lethal damage to Stem Cell DNA.

REPAIR FAILURE

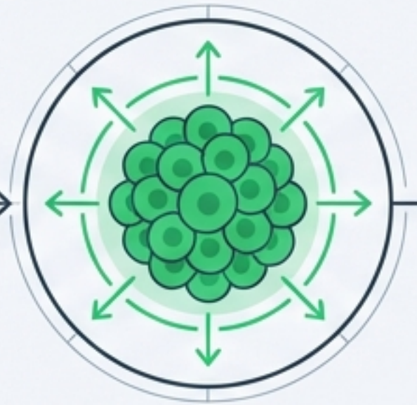
Overcomes repair mechanisms.

MUTATION



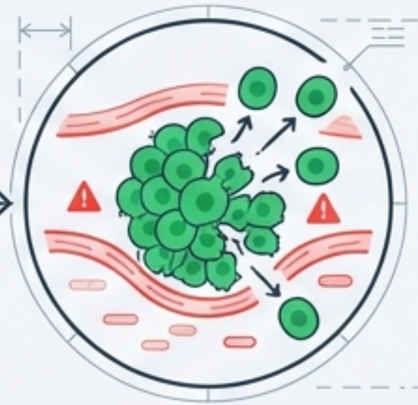
Disruption of Proto-oncogenes & Tumor Suppressors.

PROMOTION



Unregulated Division.

PROGRESSION



Invasion & Metastasis.

THE AGENTS (CARCINOGENS)

Chemicals • Viruses • Radiation

THE SABOTEURS I: CHEMICAL CARCINOGENS

Toxicology Report: Source to Target

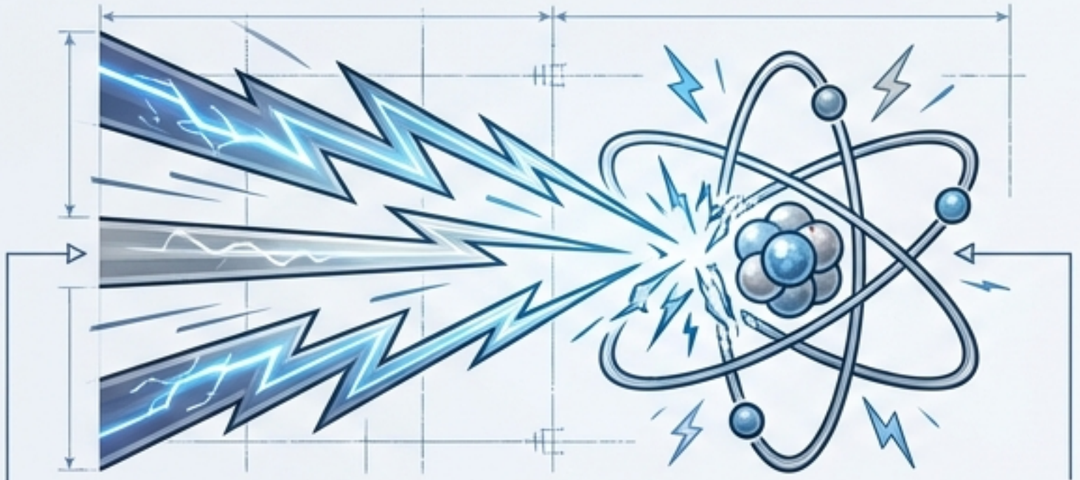
	AGENTS	TARGET PATHOLOGY
Fungal	Aflatoxins (*Aspergillus*)	Hepatocellular Carcinoma
Industrial	Vinyl Chloride (PVC)	Angiosarcoma of Liver
	Asbestos	Lung Carcinoma & Mesothelioma
	Naphthylamine	Urothelial Carcinoma
Lifestyle	Alcohol	Squamous Cell CA (Oropharynx) & Liver
	Arsenic (Cigarettes)	Skin SCC, Lung, Liver Angiosarcoma
	Nitrosamines (Smoked Foods)	Stomach Carcinoma
Iatrogenic	Alkylating Agents	Leukemia / Lymphoma

THE AGENTS (CARCINOGENS)

Chemicals • Viruses • Radiation

THE SABOTEURS II: RADIATION & VIRAL AGENTS

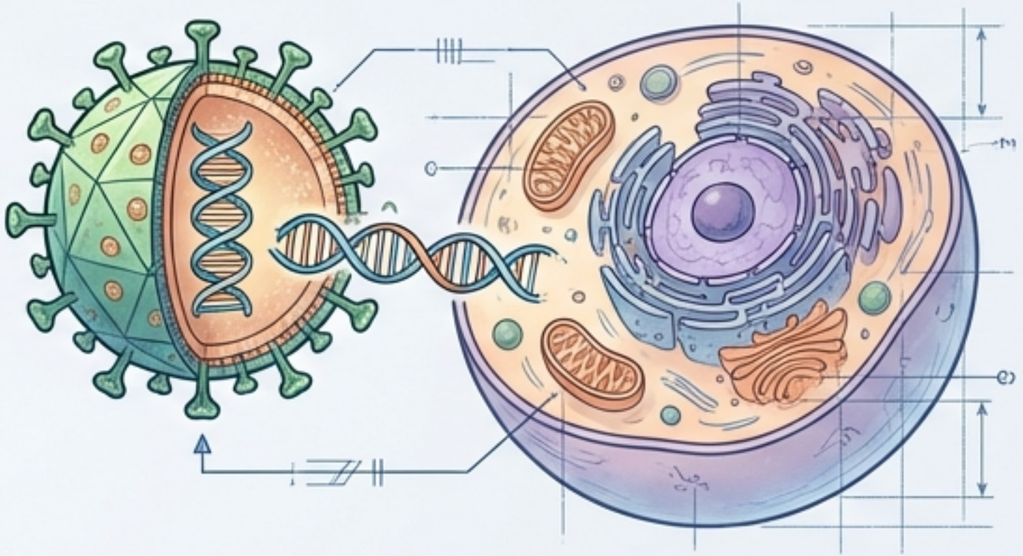
RADIATION (PHYSICS)



Ionizing Radiation (Nuclear/RT)
- Generates Hydroxyl Free Radicals — Hydroxyl Radical
- Risks: AML, CML, Papillary Thyroid CA

Non-Ionizing Radiation (UVB Sun)
- Forms Pyrimidine Dimers — Pyrimidine Dimer
- Risks: Basal Cell, Squamous Cell, Melanoma

VIRAL AGENTS (BIOLOGY)



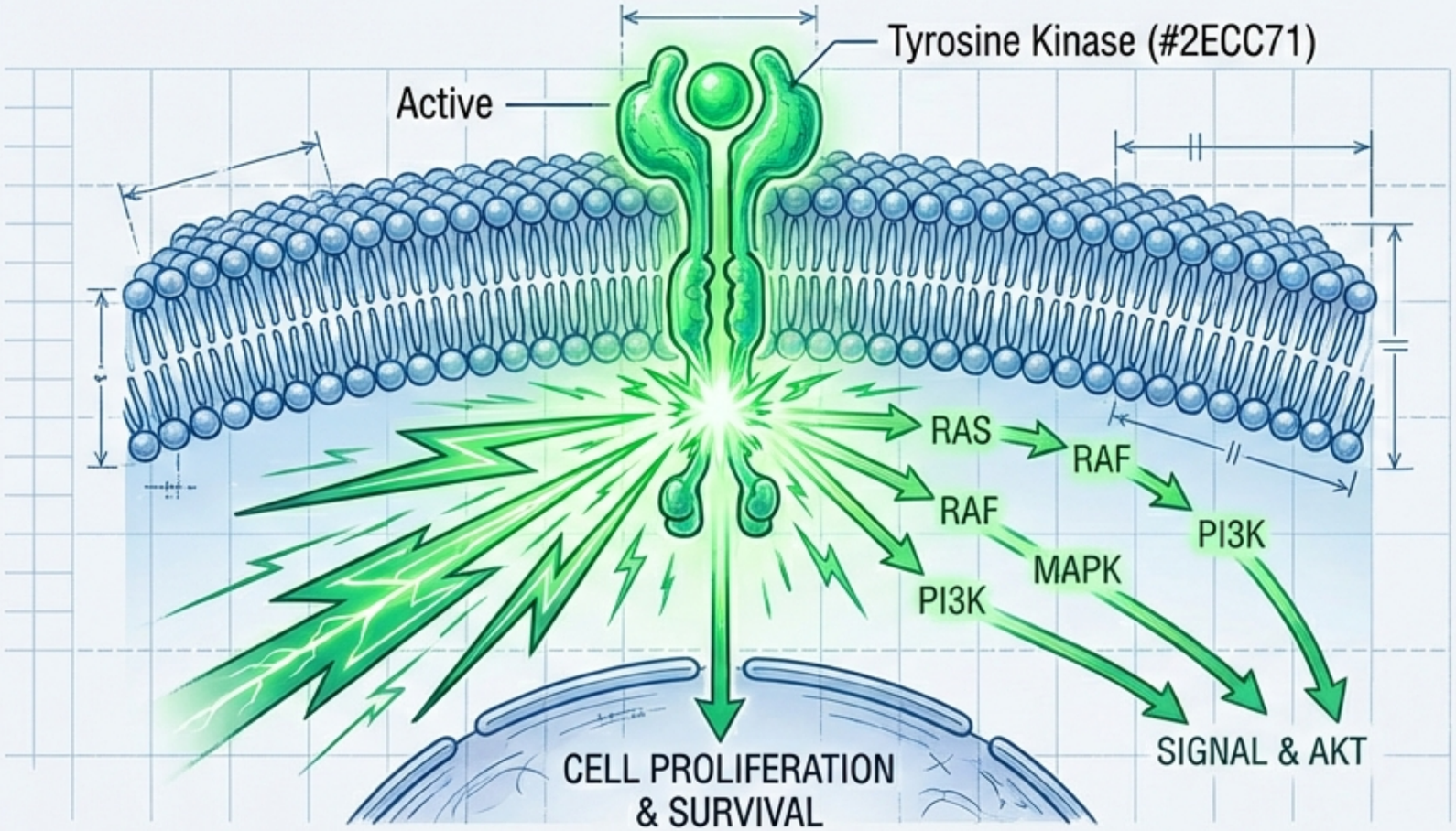
EBV → Burkitt Lymphoma, Nasopharyngeal CA
HHV-8 → Kaposi Sarcoma
HBV / HCV → Hepatocellular Carcinoma
HTLV-1 → Adult T-Cell Leukemia
HPV (16, 18, 31, 33) → Squamous Cell CA (Cervix/Anus)

THE AGENTS (CARCINOGENS)

Chemicals • Viruses • Radiation

THE ACCELERATOR STUCK ON: ONCOGENES

Growth Factors, Receptors, and Transducers



CONCEPT: Proto-oncogenes (Essential) mutate into Oncogenes (Unregulated).

MECHANISM 1: GROWTH FACTORS

PDGFB (Overexpression)
→ Astrocytoma

MECHANISM 2: RECEPTORS

ERBB2 / HER2 (Amplification)
→ Breast Carcinoma

RET (Point Mutation)
→ MEN 2A/2B, Medullary Thyroid CA

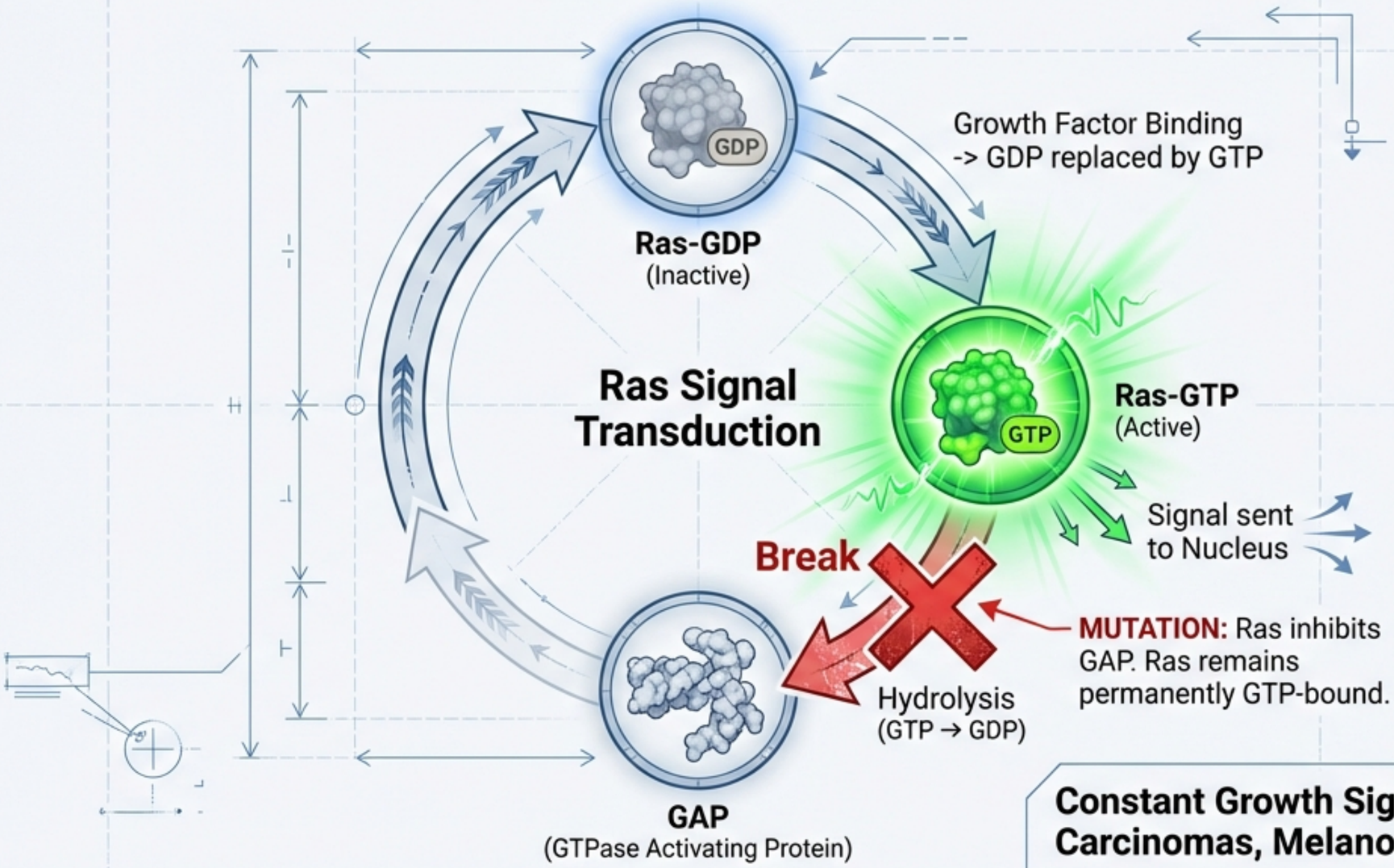
KIT (Point Mutation)
→ GI Stromal Tumor

THE AGENTS (CARCINOGENS)

Chemicals • Viruses • Radiation

THE BROKEN SIGNAL: THE RAS PATHWAY

Signal Transduction Failure



Constant Growth Signal → Carcinomas, Melanoma, Lymphoma

THE AGENTS (CARCINOGENS)

Chemicals • Viruses • Radiation

NUCLEAR & CYCLE REGULATORS

Transcriptional Control and Cell Cycle Clocks

NUCLEAR REGULATORS
(Transcription Factors)

c-MYC
→ t(8;14)
→ Burkitt Lymphoma

N-MYC
→ Amplification
→ Neuroblastoma

L-MYC
→ Amplification
→ Small Cell Lung CA

CELL CYCLE REGULATORS

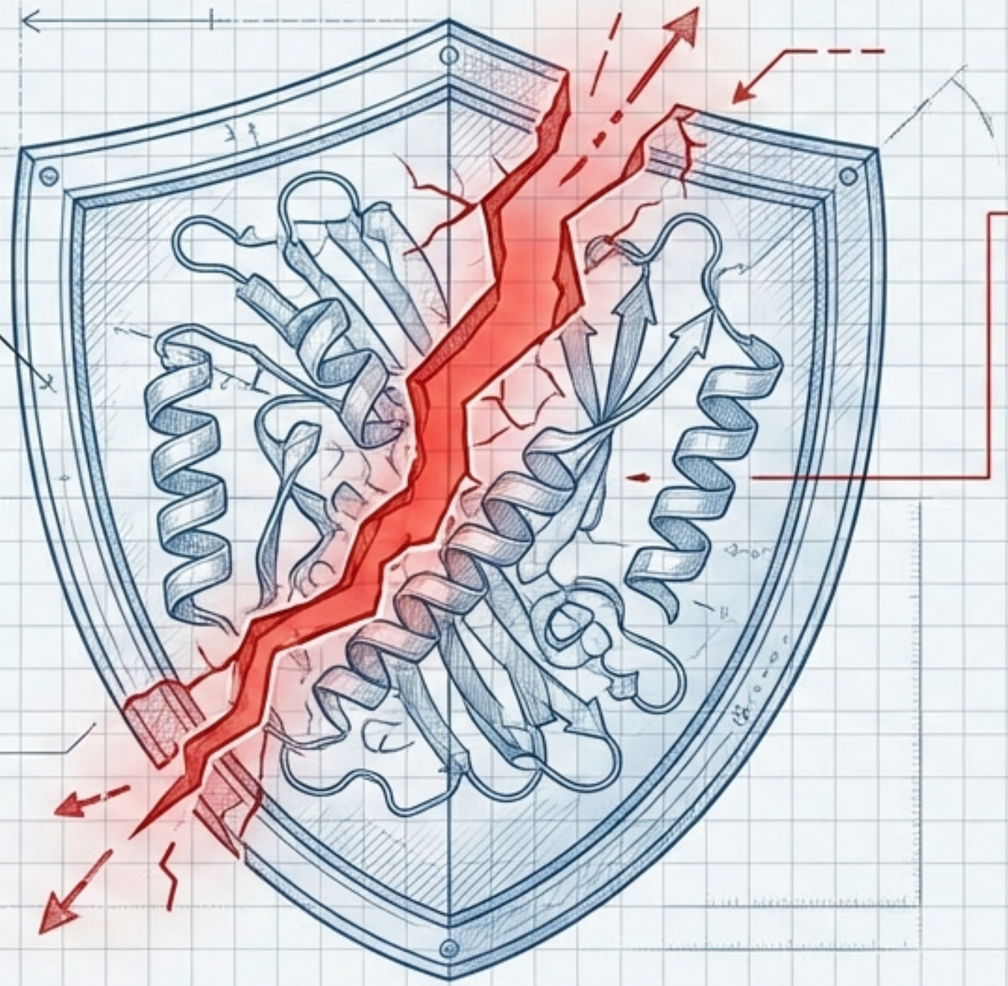
CCND1 (Cyclin D1)
→ t(11;14)
→ Mantle Cell Lymphoma

CDK4
→ Amplification
→ Melanoma

Note: Cyclin/CDK complexes phosphorylate proteins to drive the cycle.

THE BRAKES CUT: p53 TUMOR SUPPRESSOR

The Guardian of the Genome



NORMAL FUNCTION

- Regulates G1 → S Phase
- DNA Damage → p53 Slows Cycle & Repairs
- Repair Failure → p53 upregulates BAX → Apoptosis

PATHOLOGY

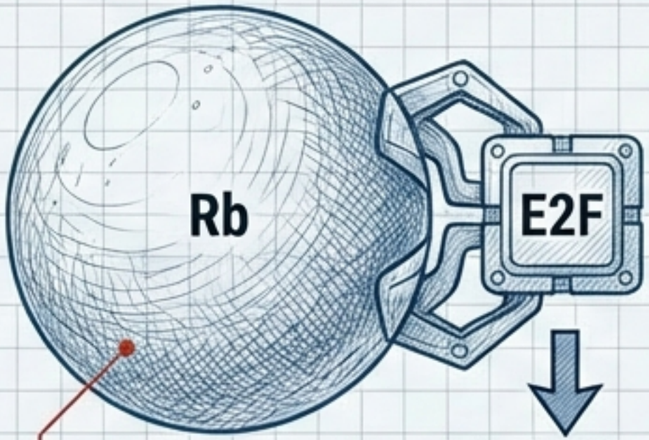
- KNUDSON TWO-HIT HYPOTHESIS: Both copies must be lost.
- Lost in >50% of all cancers.
- LI-FRAUMENI SYNDROME: Germline mutation (1st hit) + Somatic (2nd hit)
  → Multiple Carcinomas/Sarcomas.

THE GATEKEEPER BRIBED: Rb GENE

Retinoblastoma Protein and the E2F Checkpoint

Rb-E2F LATCH MECHANISM

STATE A: LOCKED

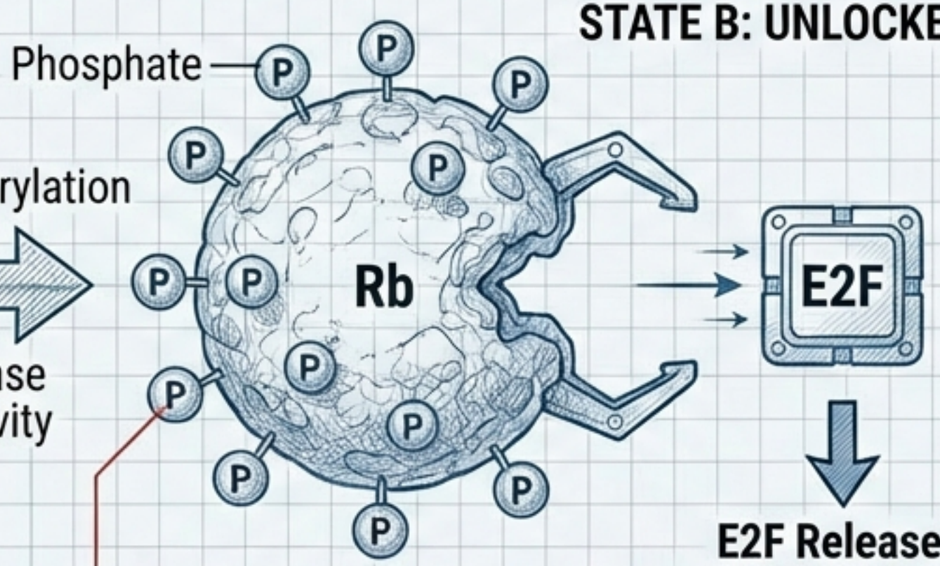


No S-Phase Progression

Phosphorylation

Kinase Activity

STATE B: UNLOCKED



E2F Released → S-Phase Begins

THE MUTATION

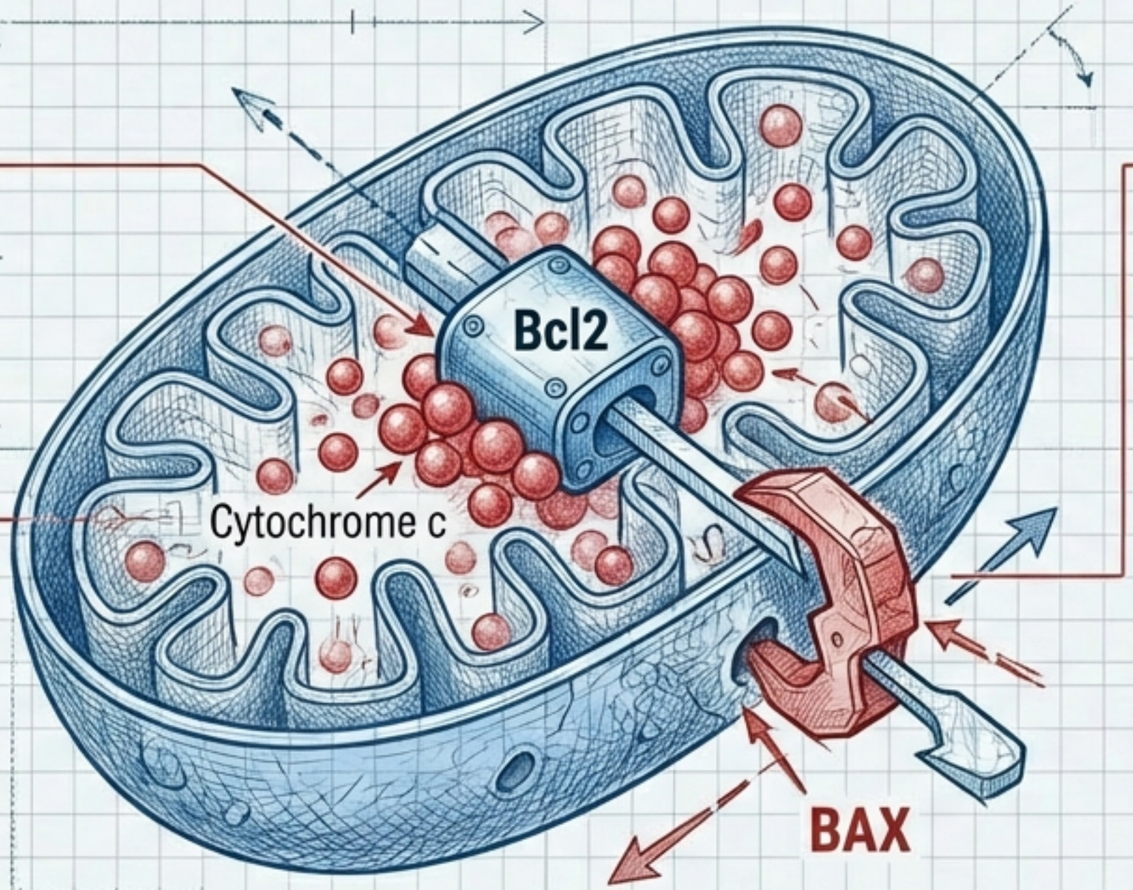
Rb fails to bind E2F
→ Constitutive Growth.

RETINOBLASTOMA

Sporadic: Unilateral tumor.
Familial: Bilateral tumor + Osteosarcoma risk.

CHEATING DEATH: Bcl2 & APOPTOSIS

The Mitochondrial Tug-of-War



MECHANISM:

Bcl2 stabilizes mitochondrial membrane, keeping Cytochrome c inside.

PATHOLOGY:

Follicular Lymphoma t(14;18)

THE EVENT:

Bcl2 moves to Ig Heavy Chain locus

↓

Massive Overexpression.

↓

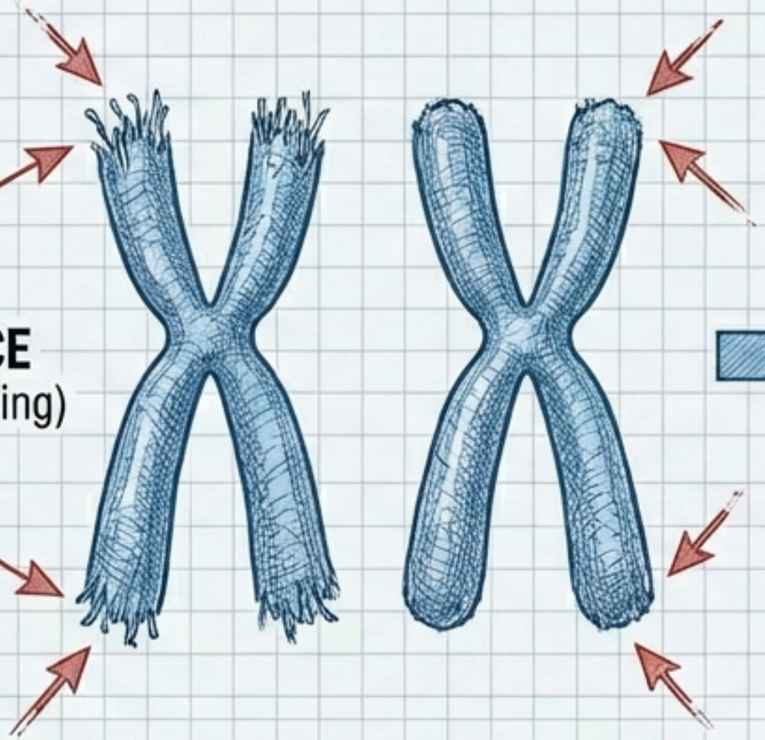
THE RESULT:

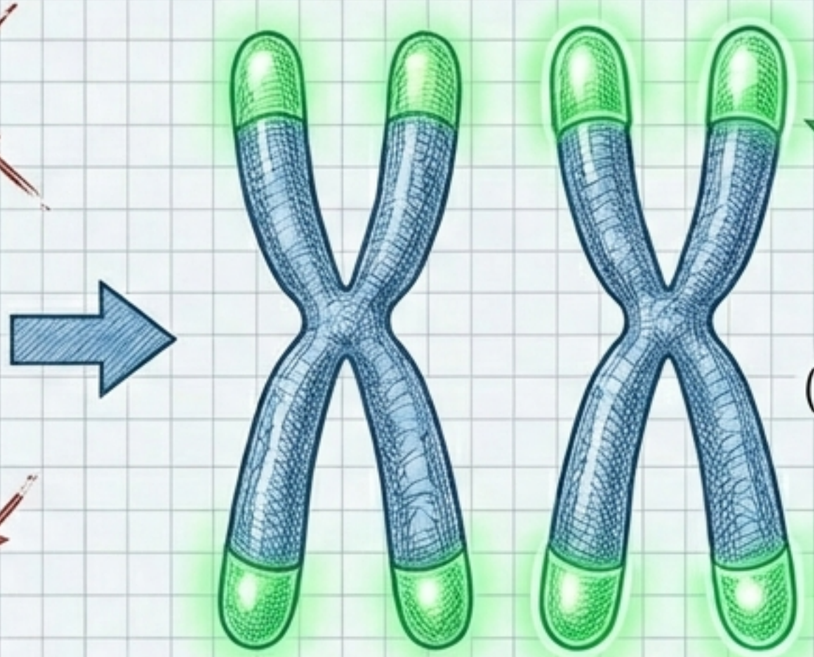
B-cells accumulate; Apoptosis is chemically blocked.

THE QUEST FOR IMMORTALITY: TELOMERASE

Evading Senescence.

SENESCENCE
(Normal Shortening)





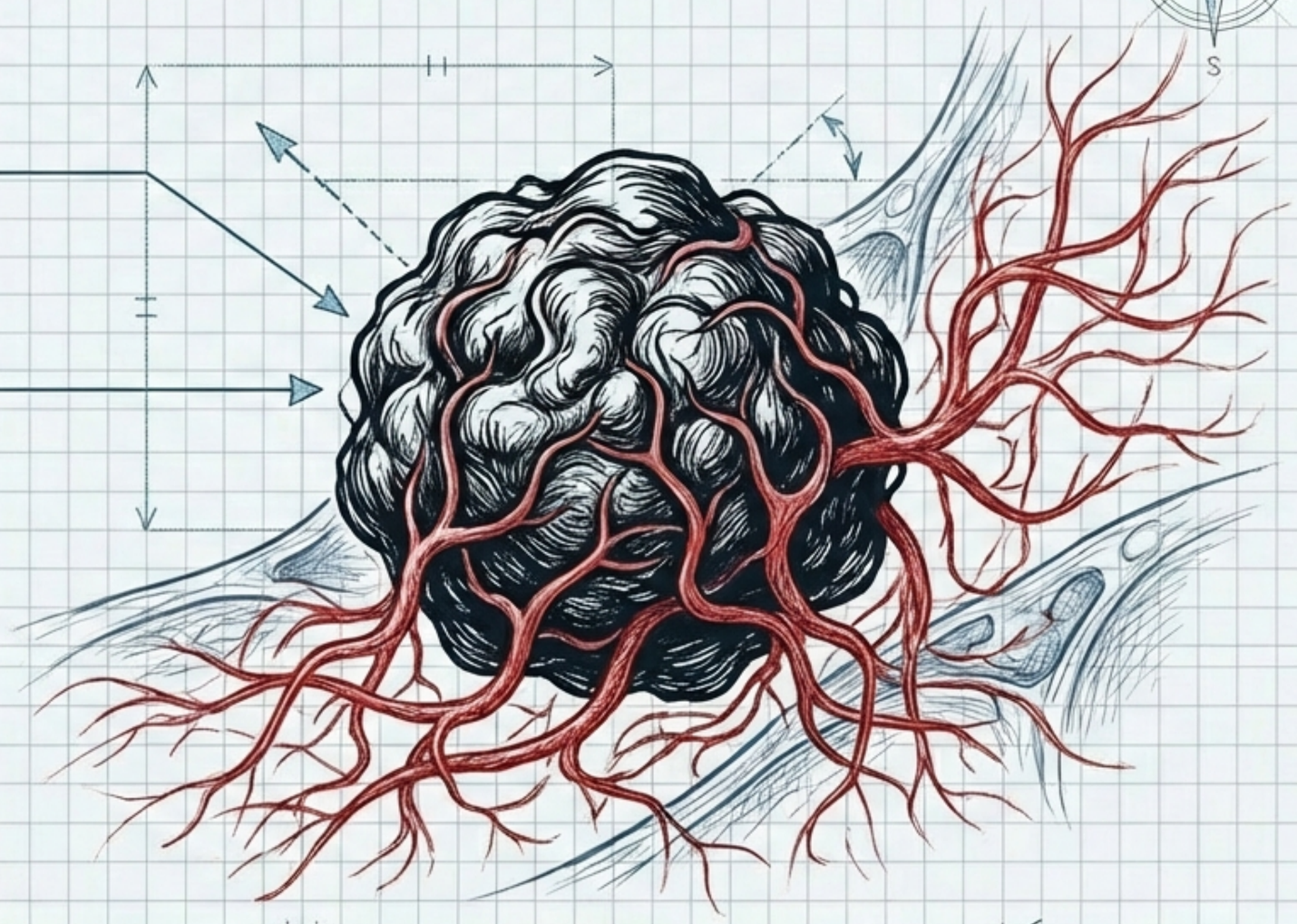
IMMORTALITY
(Telomerase Upregulated)

- **Strategy:** Cancer cells upregulate Telomerase to preserve telomere length.
- **Outcome:** Unlimited replication potential.

FEEDING THE BEAST: ANGIOGENESIS

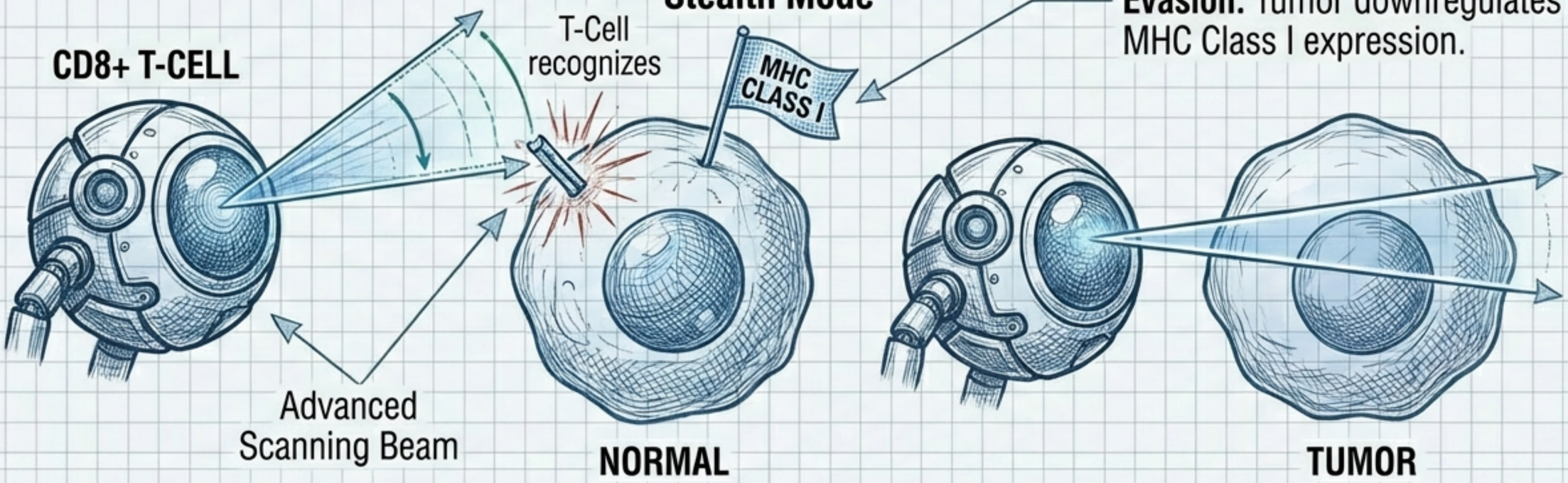
Securing Resources for Growth

- **The Limit:** Tumors cannot grow > 1-2mm without blood supply.
- **The Solution:** Production of Angiogenic Factors.
  - VEGF (Vascular Endothelial Growth Factor)
  - FGF (Fibroblast Growth Factor)



THE GREAT ESCAPE: IMMUNE SURVEILLANCE

Stealth Mechanisms



- **Normal Defense:** CD8+ T-Cells detect abnormal proteins on MHC Class I.
- **Evasion:** Tumor downregulates MHC Class I expression.
- **Result:** Invisible to cytotoxic attacks.

SUMMARY: THE HALLMARKS OF MALIGNANCY

IMMUNE EVASION
MHC I Downregulation

SELF-SUFFICIENCY
Oncogenes (Ras, HER2)

ANGIOGENESIS
VEGF

INSENSITIVITY TO ANTI-GROWTH
Tumor Suppressors (Rb, p53)

IMMORTALITY
Telomerase

EVASION OF APOPTOSIS
Bcl2 Upregulation

PRODUCER'S APPENDIX: GENETIC TRANSLOCATIONS

High-Yield Reference Data

TRANSLOCATION	ASSOCIATED MALIGNANCY	GENES INVOLVED
t(9;22)	CML (Chronic Myelogenous Leukemia)	BCR-ABL (Philadelphia Chromosome)
t(8;14)	Burkitt Lymphoma	c-MYC / Ig Heavy Chain
t(11;14)	Mantle Cell Lymphoma	Cyclin D1 / Ig Heavy Chain
t(14;18)	Follicular Lymphoma	Bcl2 / Ig Heavy Chain

Useful for rapid review and board examination preparation.