The Tumor Microenvironment and the Question of Causality

Integrating philosophical perspectives, mathematical modeling, and experimental data in oncology.

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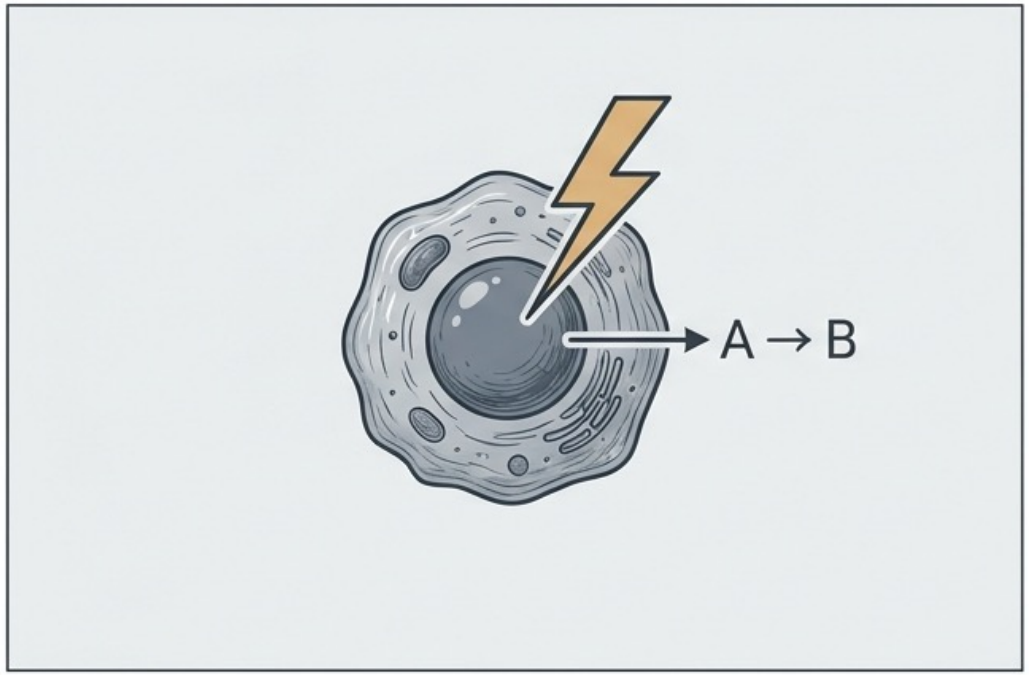
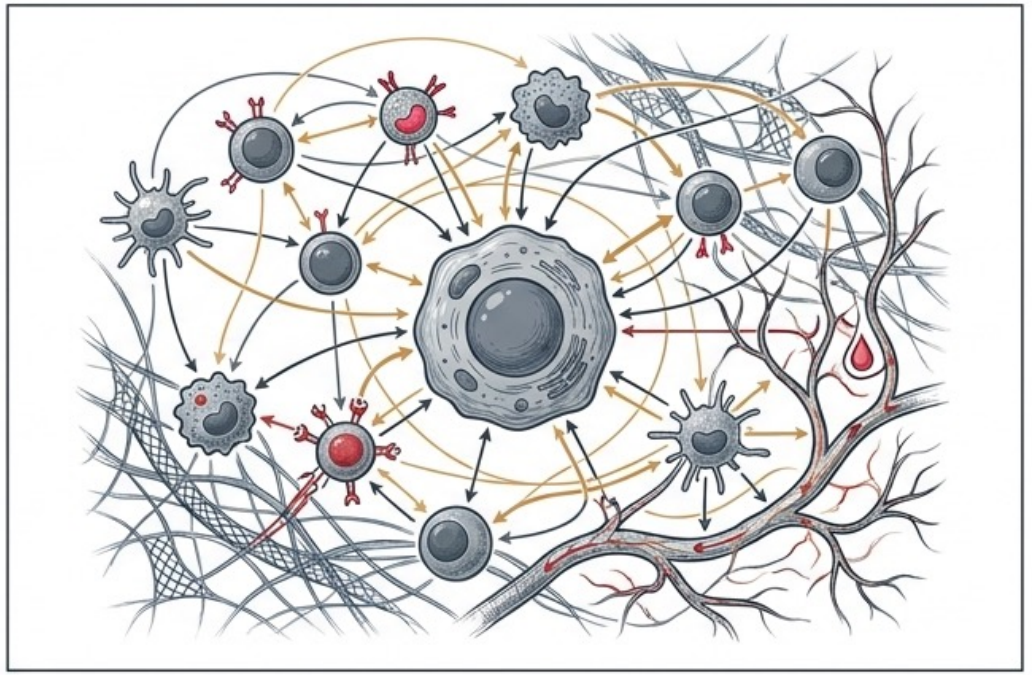
Biological complexity has outpaced our causal frameworks



Cell-Centric View. Linear causality (A → B).



TME-Centric View. High causal complexity, intra/inter-tumoral heterogeneity, and multi-scale interactions.

Identifying components of the TME is no longer enough; we must decipher the precise mechanistic pathways that cause tumor initiation and progression.

Competing frameworks require an integrated approach

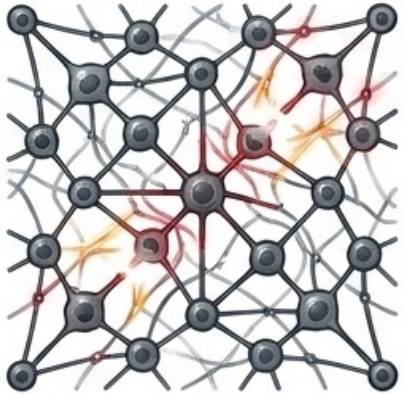
Somatic Mutation Theory (SMT)

Core Premise: Genetic mutation is the primary cause.

Locus of Control: Intracellular.

Flaw: Ignores tissue context.

Tissue Organization Field Theory (TOFT)

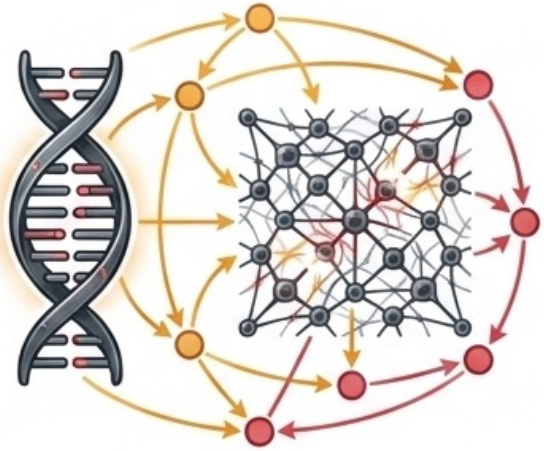


Core Premise: Disruption of tissue architecture is the primary cause.

Locus of Control: Extracellular/Microenvironmental.

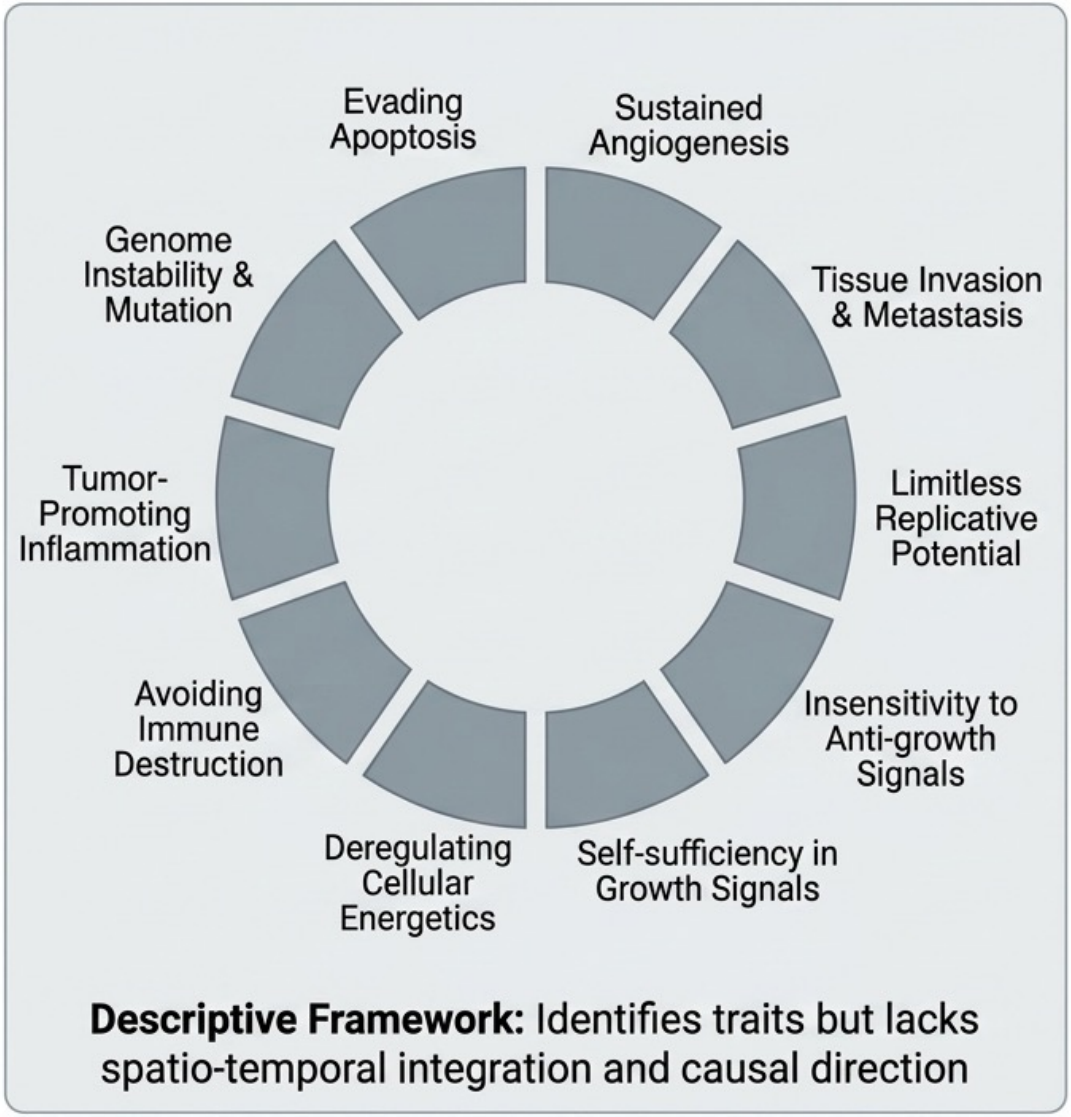
Flaw: Underplays genetic drivers.

Integrated Causal Model

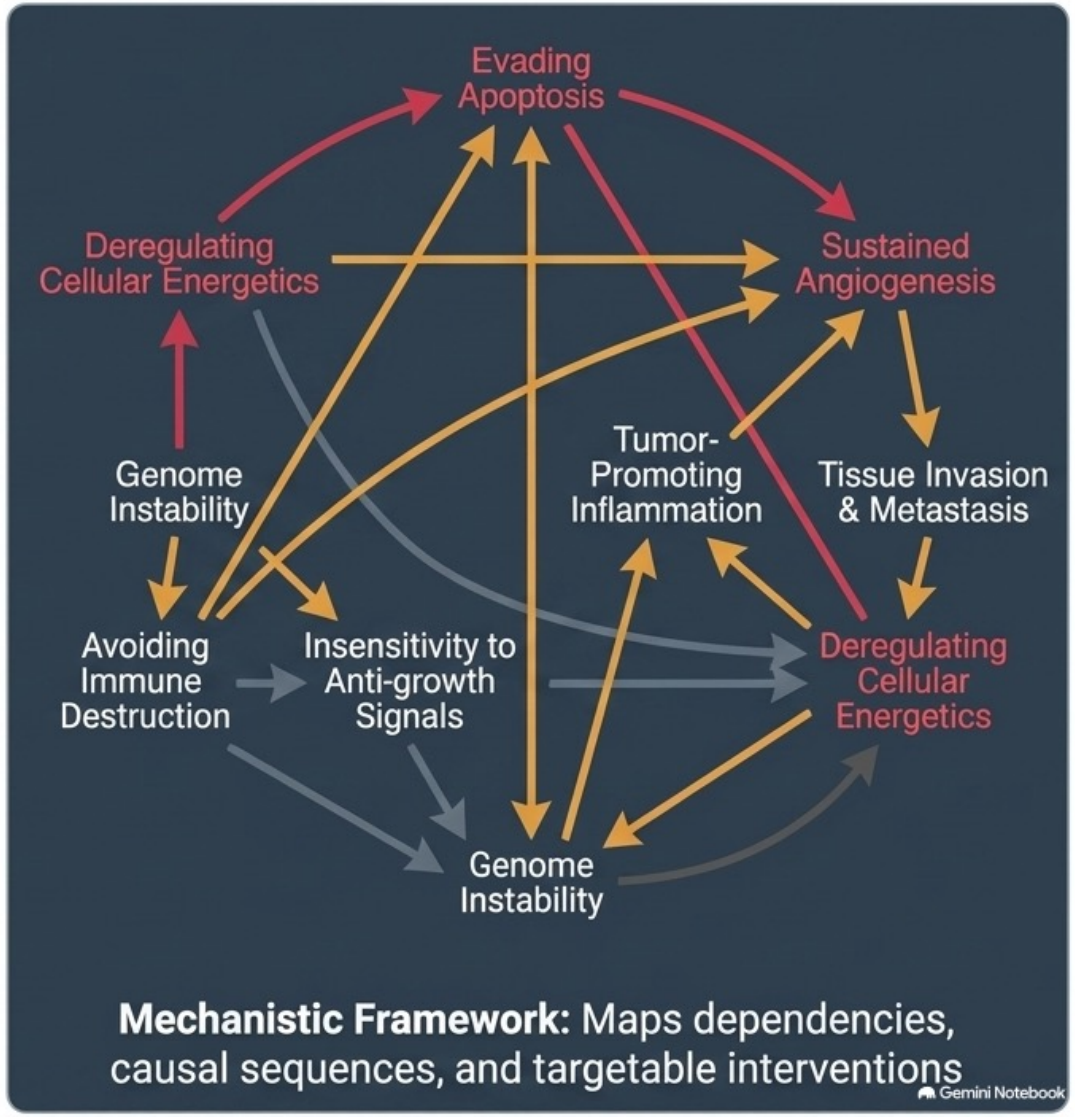


Core Premise: Tumorigenesis emerges from **probabilistic interactions** between genetic factors, cellular environment, and complexs awept in microenvironmental forces.

The "Hallmarks of Cancer" describe the what, but fail to explain the how



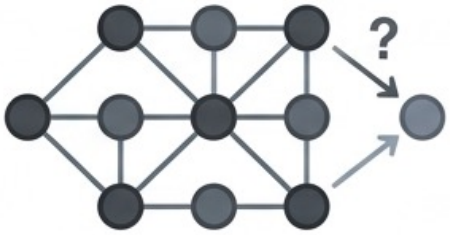
Descriptive Framework: Identifies traits but lacks spatio-temporal integration and causal direction



Mechanistic Framework: Maps dependencies, causal sequences, and targetable interventions

Modern philosophical frameworks provide the missing analytical tools

Regularity & Counterfactual



Observing constant conjunctions and asking **"what if"** a factor were removed.

Singularist

Focusing on causality within unique, unrepeatable biological events.

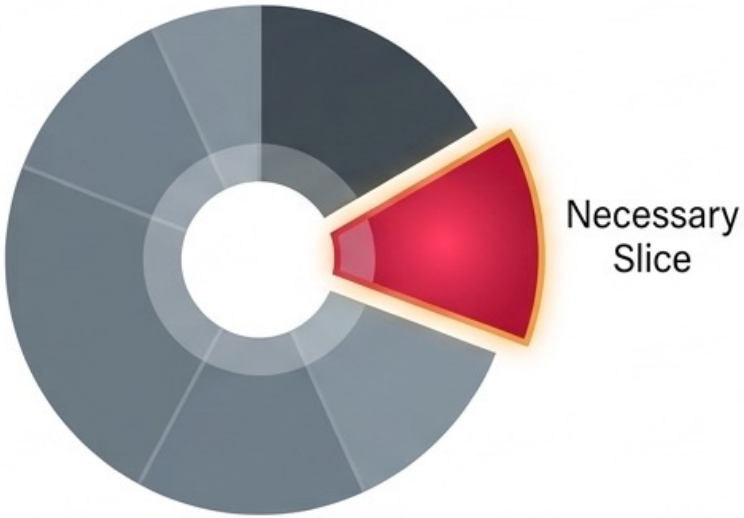
Interventionist (Woodwardian)

A cause is something that, when manipulated, **systematically alters the effect**.

To untangle the TME, we must shift from identifying associations to **identifying targets** for intervention.

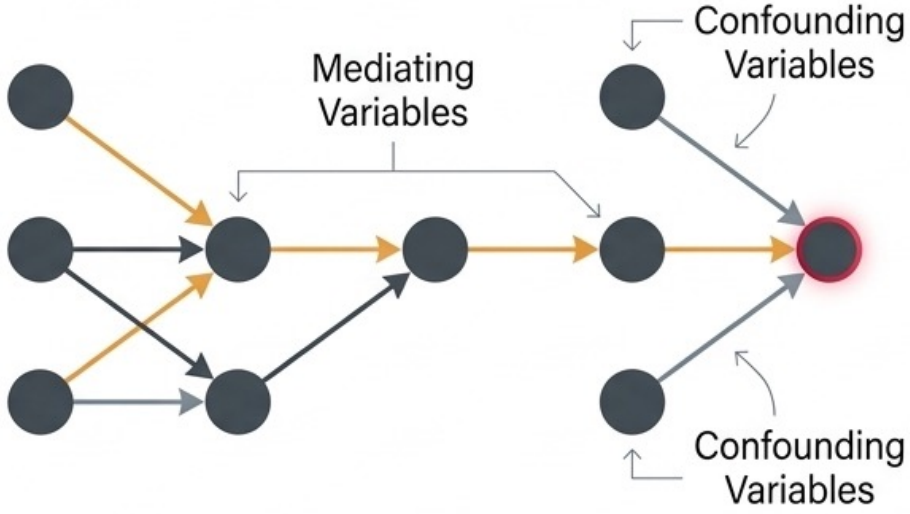
Translating philosophical causality into biological mapping

The Causal Pie



No single factor acts alone. We identify specific necessary slices within broader sufficient mechanisms.

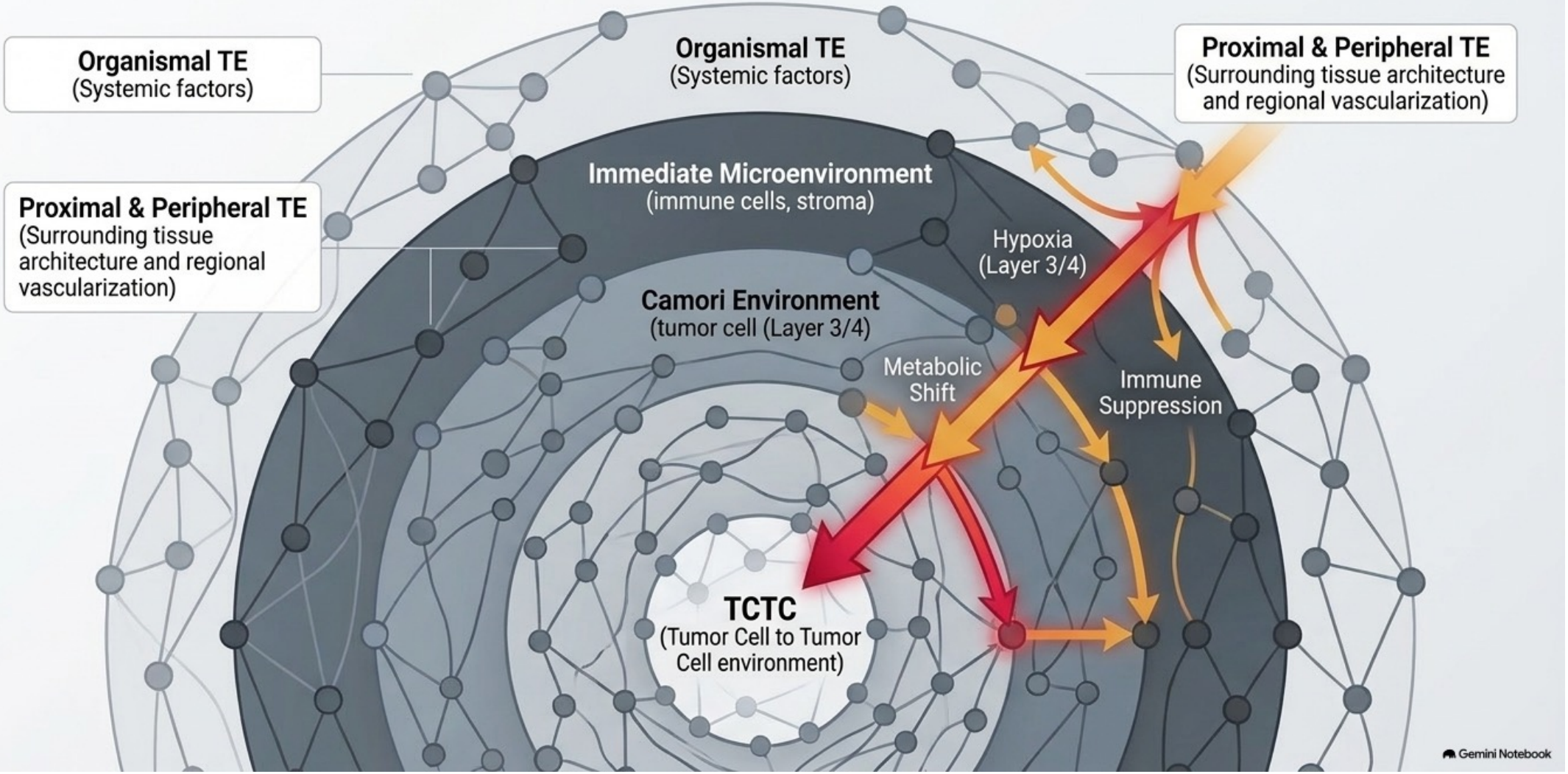
Directed Acyclic Graphs (DAGs)



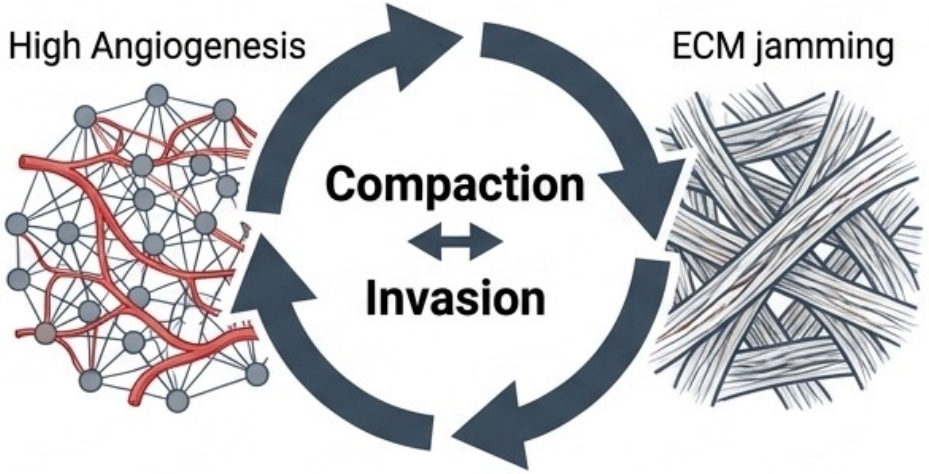
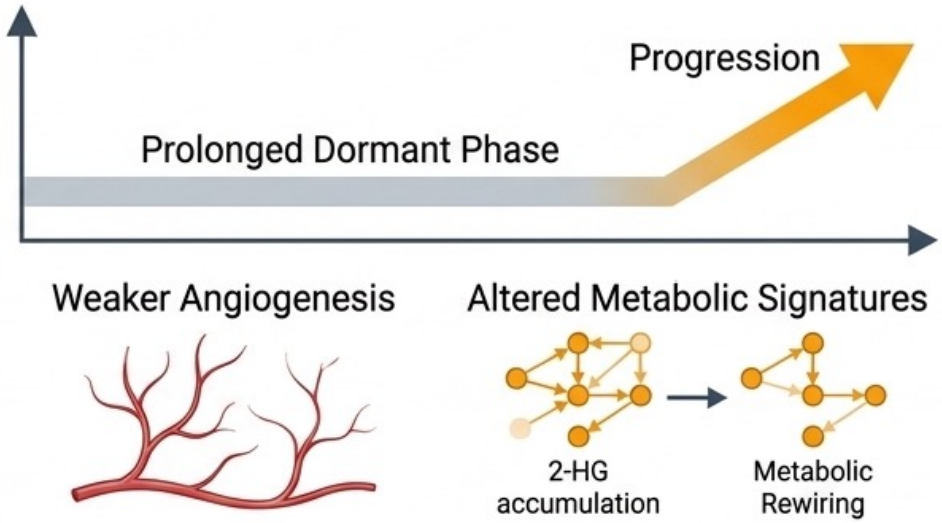
Maps dependencies and causal sequences without circular feedback loops to isolate direct effects.

These tools differentiate active causal drivers from mere accompanying factors within the microenvironment.

The Tumor Microenvironment acts as a multi-scale causal network

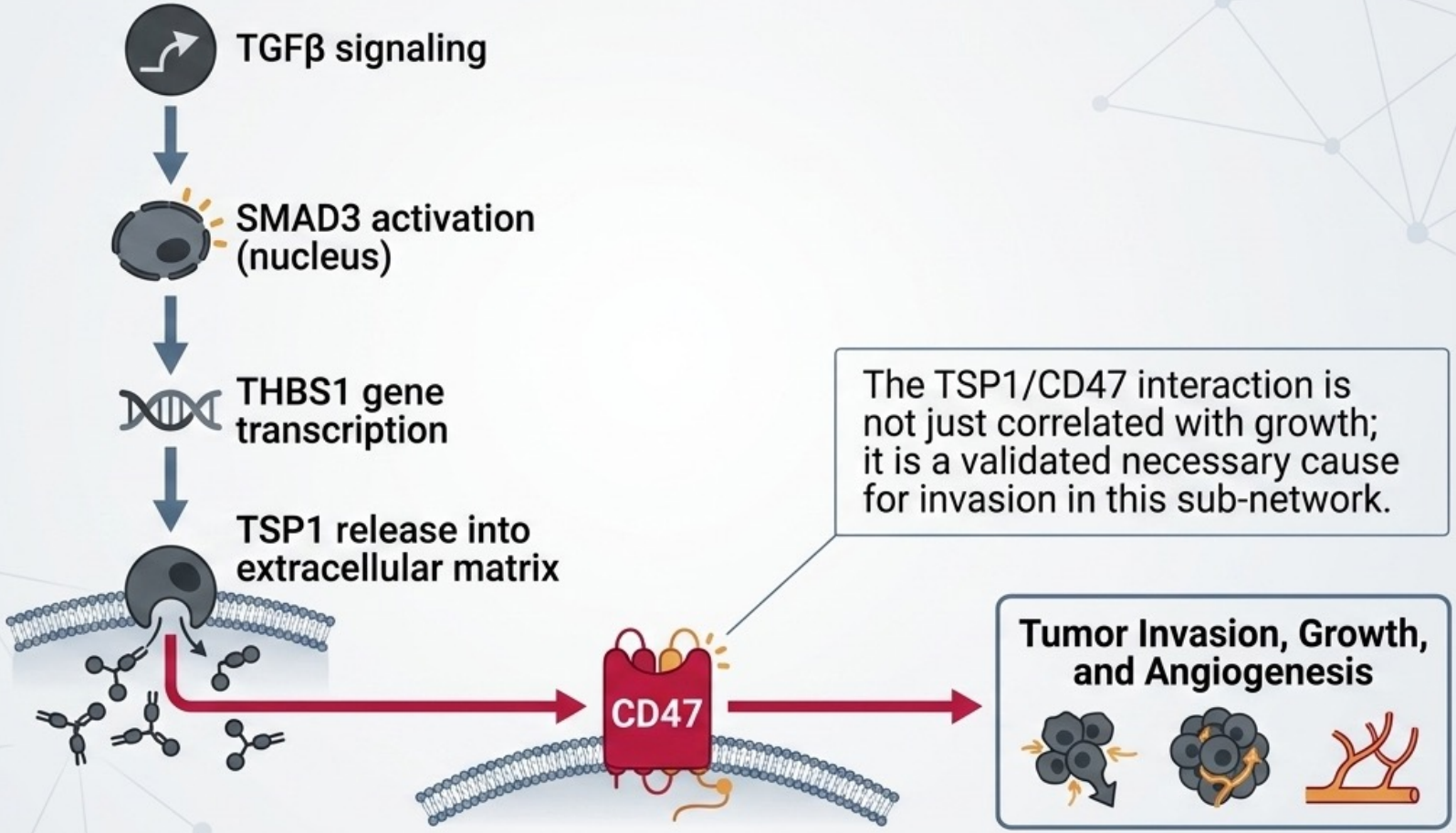


Case Study I: Distinct causal dynamics in Diffuse Gliomas

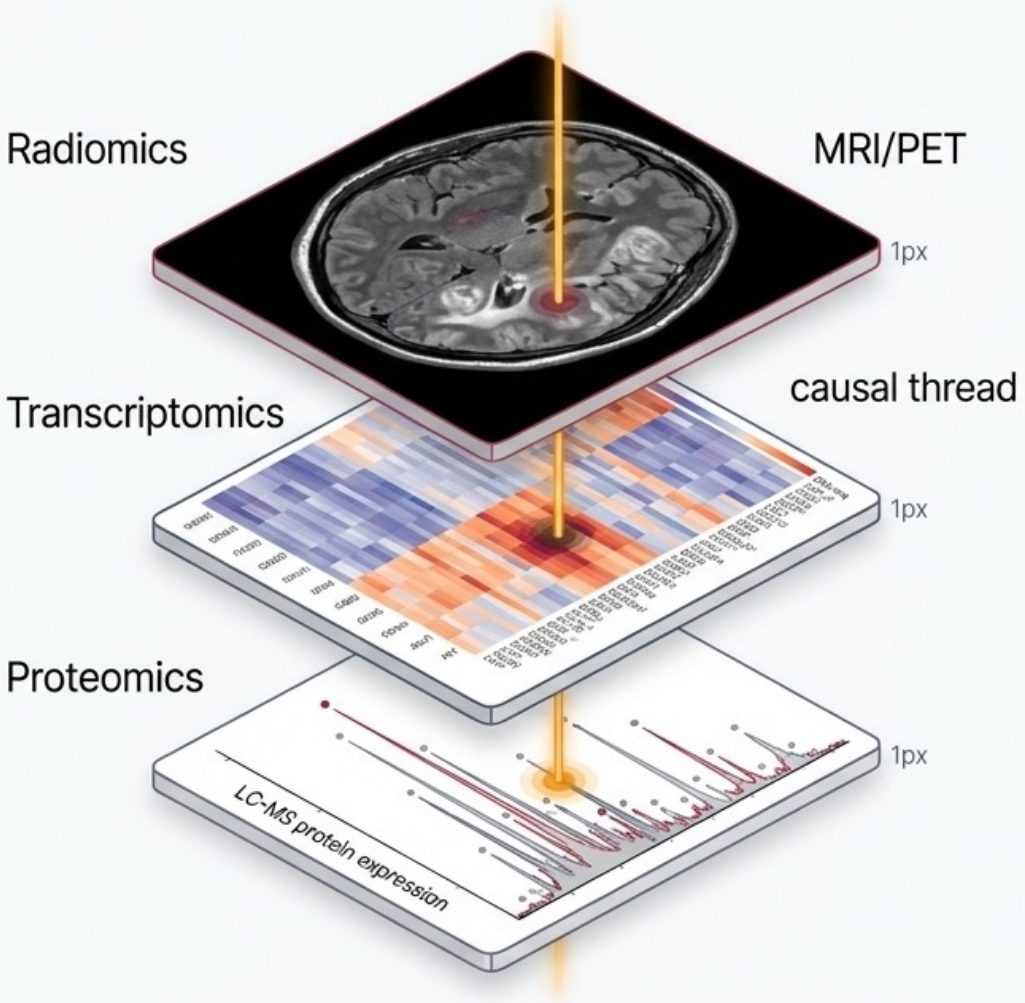
IDH-Wildtype (Glioblastoma)	IDH-Mutant Glioma
	
High speed, aggressive progression.	Slower progression, metabolic rewiring.

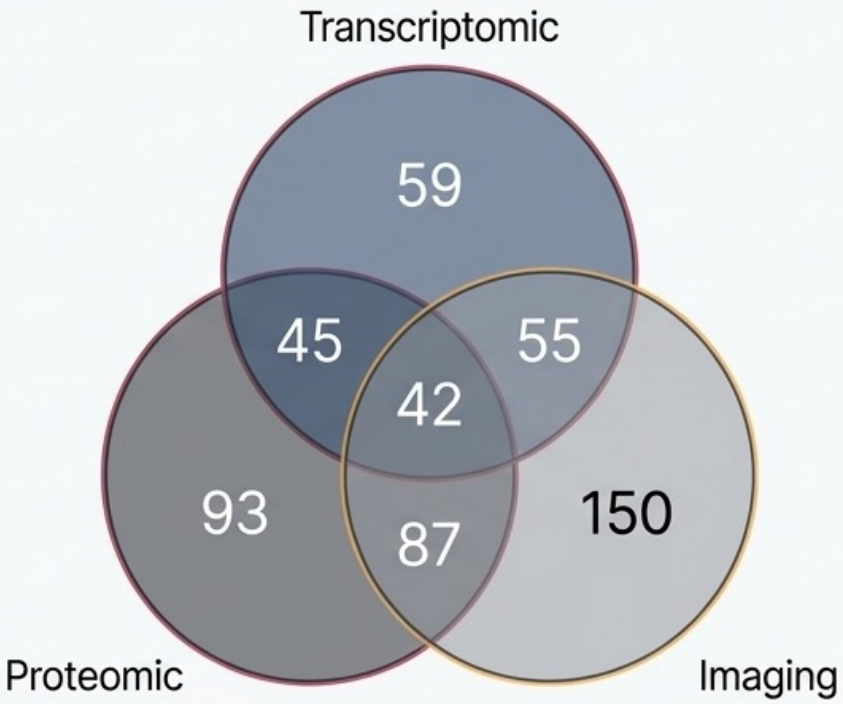
Different genetic origins (*IDH status*) completely rewire the microenvironmental causal web, demanding distinct interventional logic.

Thrombospondin-1 (TSP1) drives invasion in Glioblastomas



Predicting recurrence in IDH-Mutant gliomas requires multi-modal integration





By cross-analyzing imaging signatures with molecular data, we isolate the true causal drivers of recurrence from background biological noise.

Case Study II: The VHL mutation cascade in Clear Cell Renal Carcinoma

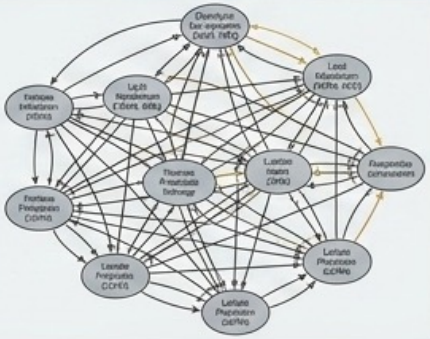
(Primary necessary cause)

VHL Inactivation

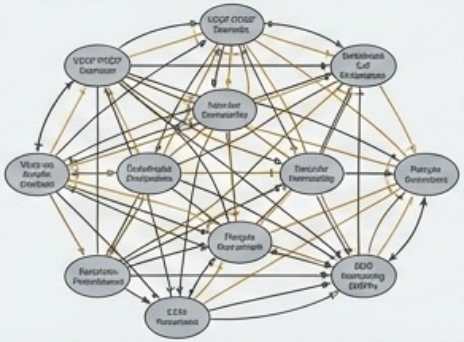
↓

HIF1/2 Stabilization

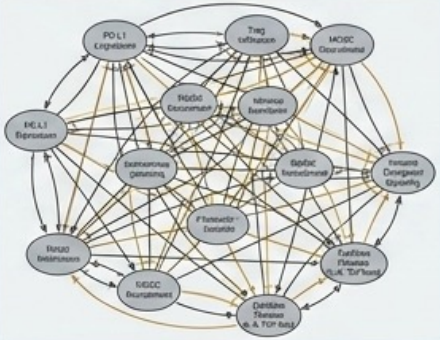
Metabolic Module



Stromal/Angiogenic Module

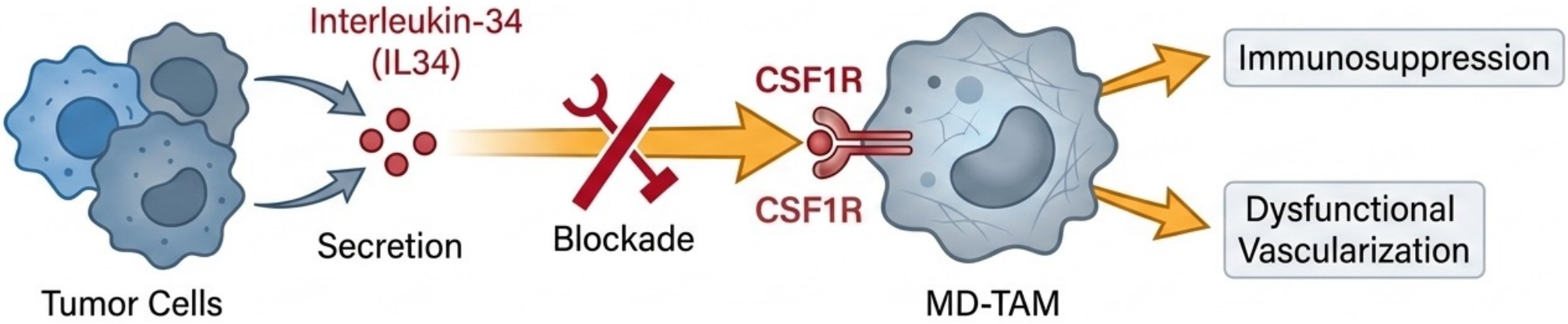


Immune Module



RCC is causally dominated by a single genetic inactivation that instantly rewires interdependent microenvironmental networks, demanding hierarchical probabilistic modeling.

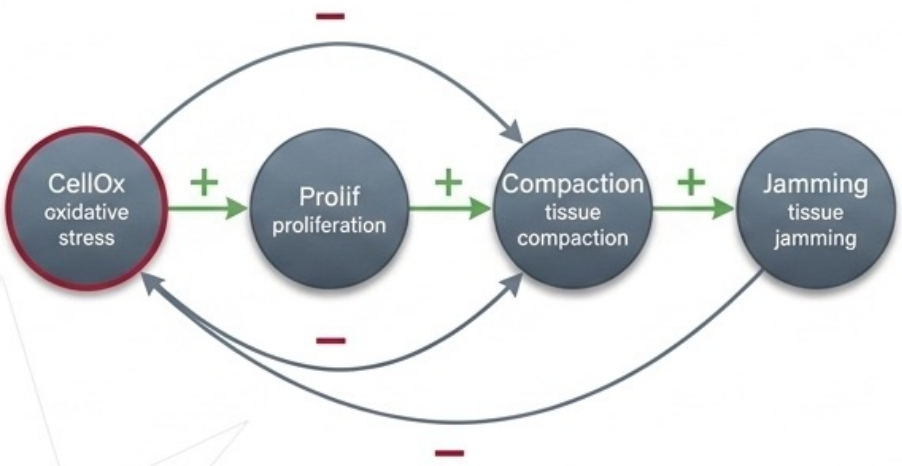
The IL34/CSF1R axis: A targetable driver of immunosuppression



Pharmacological blockade of this specific causal axis reverses immunosuppression and improves the efficacy of standard treatments.

Validating causal webs requires mathematical modeling

Conceptual Directed Acyclic Graph (DAG)



Mathematical Implementation & Simulation

```
from scipy.integrate import solve_ivp
import matplotlib.pyplot as plt

# ... (omitted comments) ...

src
def f(t, y):
    CellOx, Prolif, Compaction, Jamming, Tumor = tuple(y)
    n = 3
    dCellOx = (0.1/(1+2*Compaction) / (0.1+CellOx**2) - ( CellOx * ( Compaction**n / (2
    dProlif = CellOx*1.4 - Prolif
    dCompaction = Compaction * (Prolif/7 - 1.5*Jamming)
    #Prolif+(Prolif / (Prolif ** 2 +1) / (0.5+Compaction**2) \
    #   - Compaction+10*(Jamming**n / (2**n + Jamming**n))
    dJamming = Jamming * (Compaction*2 - 1.1)
    dTumour = Compaction/10
    return [dCellOx, dProlif, dCompaction, dJamming, dTumour]

names = ["CellOx", "Prolif", "Compaction", "Jamming", "Tumour size"]
t = 120
init = np.array([9,0,1e-5,1e-5,0])
sol = solve_ivp(f, (0, t), init, t_eval=np.linspace(0, t, 500))
plt.figure(figsize=plt.figaspect(0.5))
plt.plot(sol.t, sol.y.T[:,:4])
plt.legend(names);
```

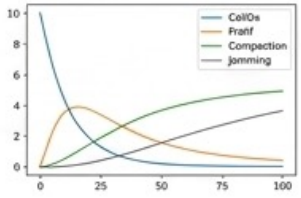
$$\text{dCellOx} = \frac{0.1/(1+2*\text{Compaction})}{0.1+\text{CellOx}**2} - \left(\frac{\Psi \cdot \text{Compaction}**n}{(2)} / \frac{2}{120}\right);$$

$$\text{dProlif} = \text{CellOx}*1.4 - \text{Prolif};$$

$$\text{dCompaction} = \text{Compaction} * (\text{Prolif}/7 - 1.5*\text{Jamming});$$

$$\text{dJamming} = \text{Jamming} * (\text{Compaction}**2 - 1.1);$$

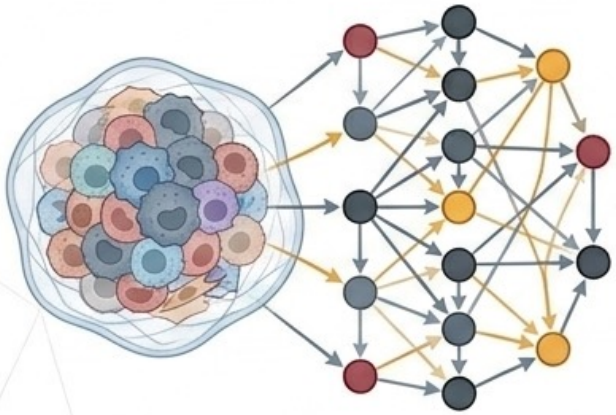
$$\text{dTumour} = \text{Compaction}/10$$



We cannot test every interaction in vivo. Structural Equation Modeling (SEM), Bayesian networks, and differential equations allow us to build “possible worlds” and estimate path coefficients, transforming static diagrams into dynamic, testable biological simulations.

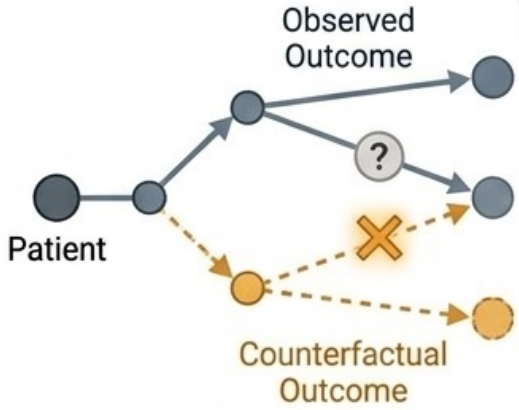
From philosophy to the patient: cligrapify to the patient: Clinical implications of causal models

Network Visualization → **Woodwardian Intervention** → **Counterfactual Clinical Trials**



Using multi-cellular organoids to map patient-specific TME networks.

Simulating virtual interventions on the causal graph to predict therapeutic effects, separating direct from indirect responses.



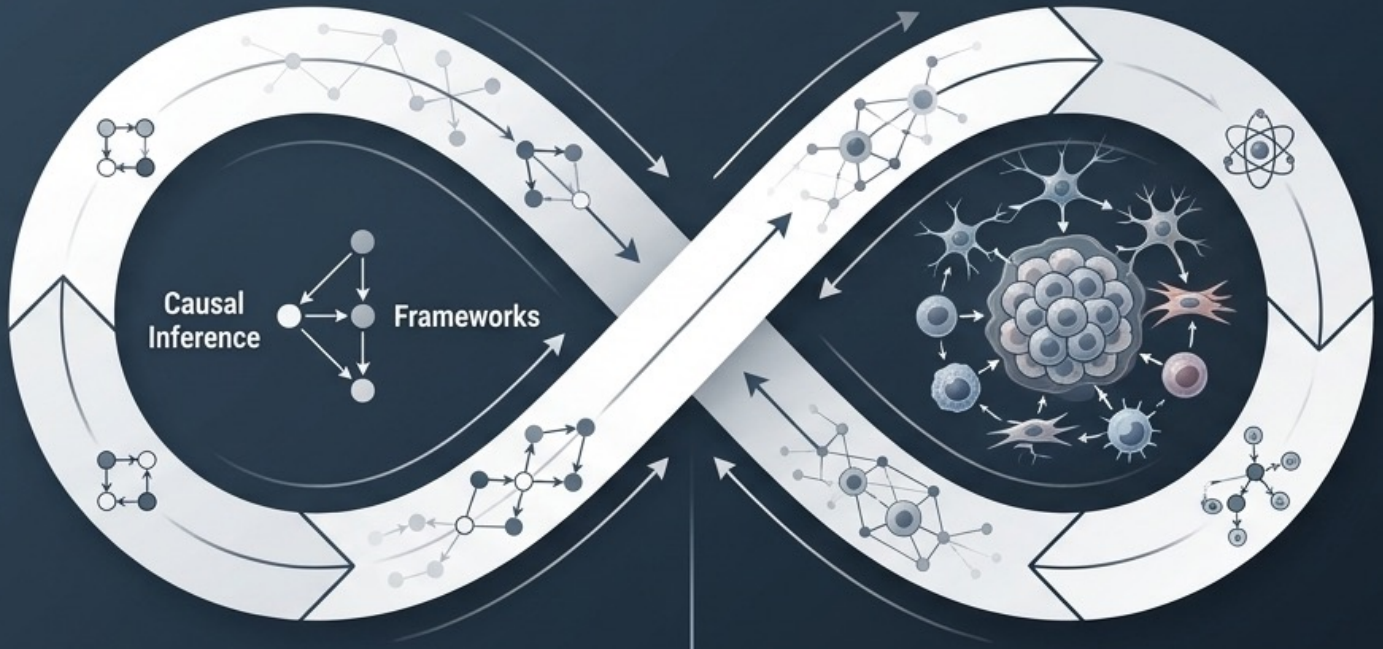
Enhancing trial design by using mathematical models to ask "What would have happened to this specific patient if X pathway was blocked?"

Causal modeling shifts personalized medicine from purely genetic profiling to holistic, microenvironmental network targeting.

Closing the loop: Biomedicine and Philosophy in dialogue

Philosophy enriches **Science**

Provides conceptual rigor, distinguishes causes from conditions, and offers frameworks (DAGs, INUS) to navigate the chaotic data of of the Tumor Microenvironment.



Science enriches **Philosophy**

The biological reality of the TME tests the limits of metaphysical theories, proving that strict single-cause models fail in the face of multi-scale, heterogenous living systems.

"A holistic, interdisciplinary approach is essential. Identifying associations is merely observation; charting causality is the prerequisite for a cure."