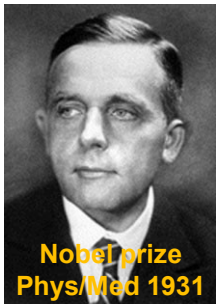

Otto Warburg found 1924: Cancer cells also do anaerobic glycolysis

Evidence for an Alternative Glycolytic Pathway in Rapidly Proliferating Cells

Matthew G. Vander Heiden,[1,2,3]* Jason W. Locasale,[2,3] Kenneth D. Swanson,[2] Hadar Sharfi,[2] Greg J. Heffron,[4] Daniel Amador-Noguez,[5] Heather R. Christofk,[2] Gerhard Wagner,[4] Joshua D. Rabinowitz,[5] John M. Asara,[2] Lewis C. Cantley[2,3]†

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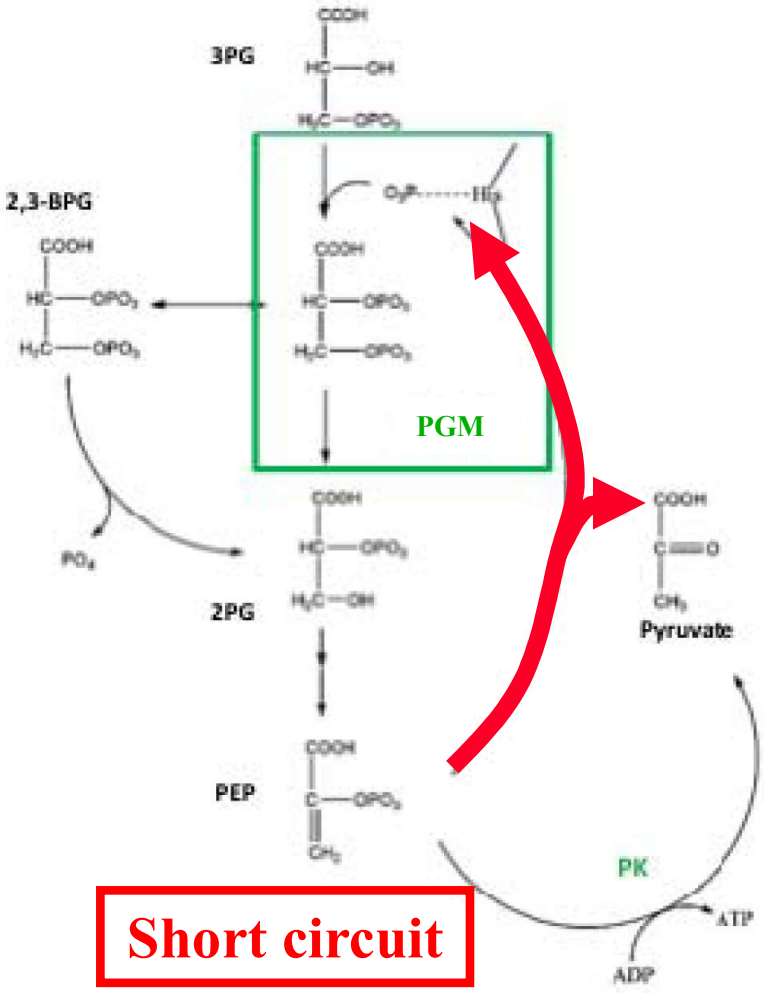
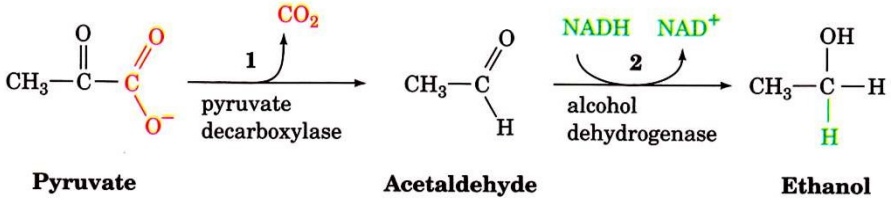


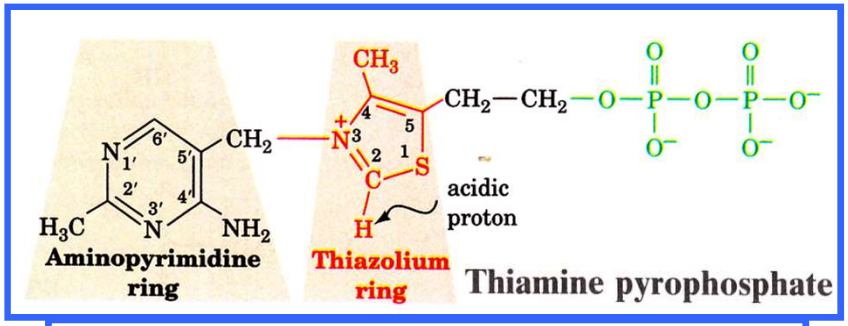
- **Warburg's Observation:** Cancer cells need a lot of anabolism and thus glycolysis to produce pyruvate as anabolic intermediate, but often have reduced pyruvate kinase (PK) activity – why?

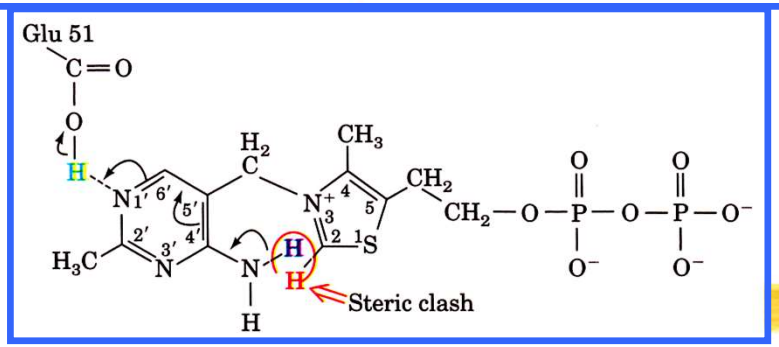
- **Modern Answer:** In cancer cells PEP's phosphate transfers to phosphoglycerate mutase (PGM) where it eventually hydrolyses so that the cell avoids producing ATP from excess PEP, which would allosterically downregulate glycolysis!

Yeast upon oxygen depletion: Alcoholic fermentation

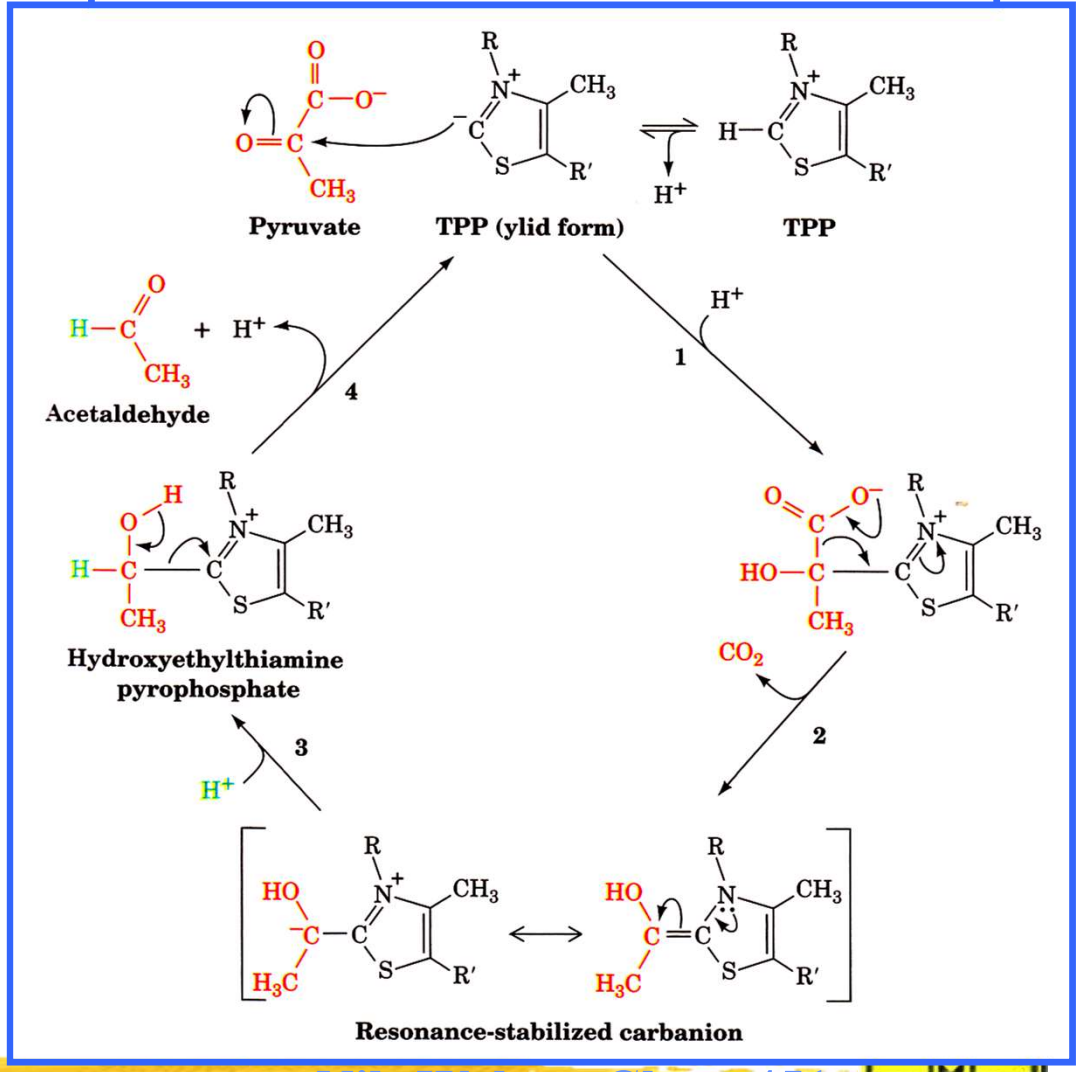
Goal: Getting rid of NADH







Decarboxylation mechanism

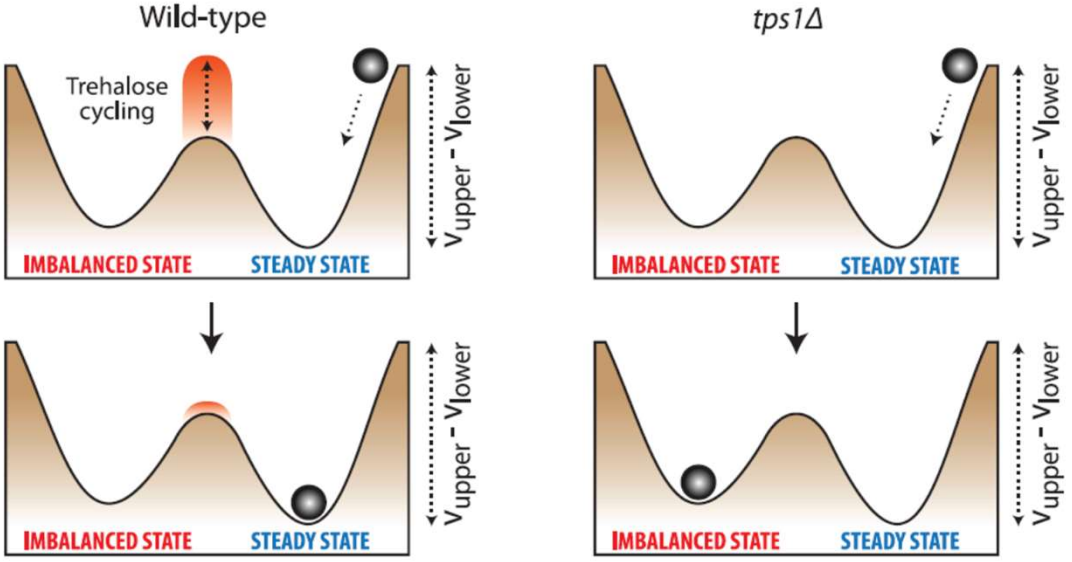


Yeast glycolysis is programmed to become imbalanced in some cells

Lost in Transition: Start-Up of Glycolysis Yields Subpopulations of Nongrowing Cells

Johan H. van Heerden,[1,2,3] Meike T. Wortel,[1,2,3] Frank J. Bruggeman,[1,3] Joseph J. Heijnen,[2,4] Yves J. M. Bollen,[3,5] Robert Planqué,[6] Josephus Hulshof,[6] Tom G. O'Toole,[7] S. Aljoscha Wahl,[2,4] Bas Teusink[1,2,3]*

Cells need to adapt to dynamic environments. Yeast that fail to cope with dynamic changes in the abundance of glucose can undergo growth arrest. We show that this failure is caused by imbalanced reactions in glycolysis, the essential pathway in energy metabolism in most organisms. The imbalance arises largely from the fundamental design of glycolysis, making this state of glycolysis a generic risk. Cells with unbalanced glycolysis coexisted with vital cells. Spontaneous, nongenetic metabolic variability among individual cells determines which state is reached and, consequently, which cells survive. Transient ATP (adenosine 5′-triphosphate) hydrolysis through futile cycling reduces the probability of reaching the imbalanced state. Our results reveal dynamic behavior of glycolysis and indicate that cell fate can be determined by heterogeneity purely at the metabolic level.



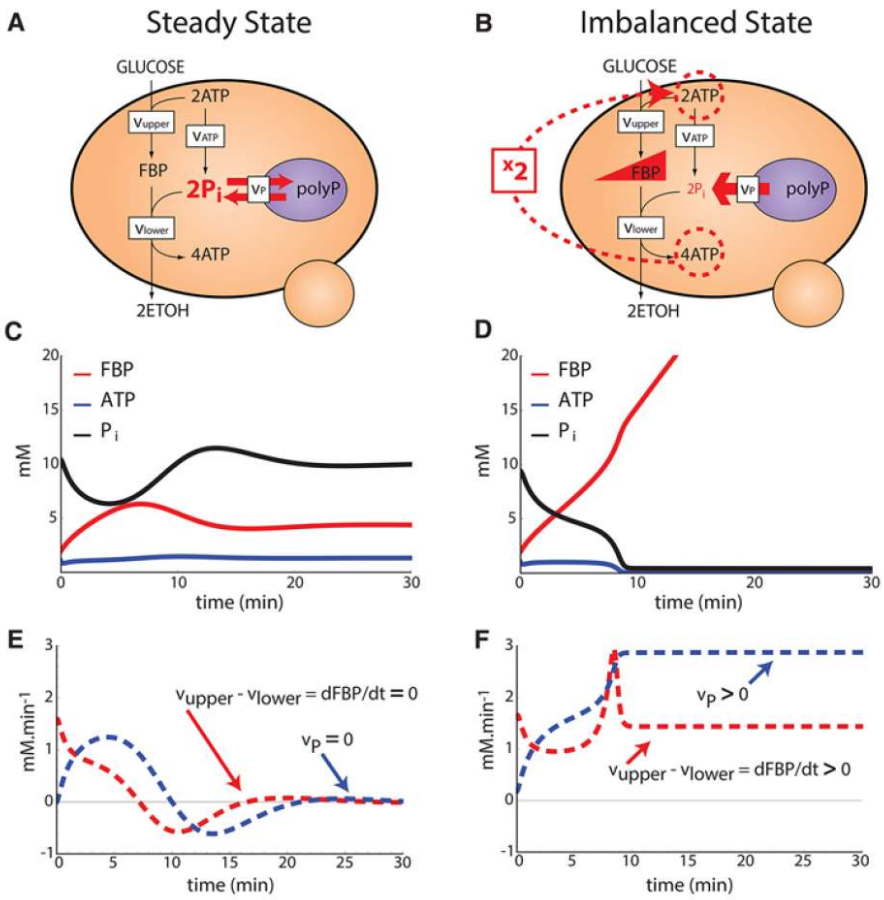


Fig. 4. Generalized core model of glycolysis can reach two stable, co-existing, states. The left panel shows the global steady state, the right panel the imbalanced state. The difference between panels is the initial P_i level (10.4 and 9.4, respectively). (**A** and **B**) Stoichiometry of the core model, with red arrows emphasizing the vacuolar flow of P_i from polyphosphates (polyP). The coupling between the upper and lower part of glycolysis through ATP is emphasized by the red dashed line (B). (**C** and **D**) Metabolite levels for a simulation of the core model, resulting in steady state (metabolite levels constant in time, C) or imbalance (FBP accumulation at very low P_i and ATP levels, D). (**E** and **F**) characteristic rates that specify the states: the red dashed lines indicate the difference in rate between upper and lower glycolysis ($v_{upper} - v_{lower}$), which is zero at steady state (E) and is positive at the imbalanced state (F). The dashed blue lines represent the vacuolar import rate of P_i (v_P), which should be zero at steady state. In Fig. 4F, the constant positive v_P indicates mobilization of P_i, which sustains accumulation of FBP (red dashed line) through the stoichiometric coupling of ATP.

SCIENCE VOL 343 28 FEBUARY 2014

Chapter 17: What have we learned?

☺ Glycolysis phosphorylates glucose and splits it into 2 C_3 sugar phosphates

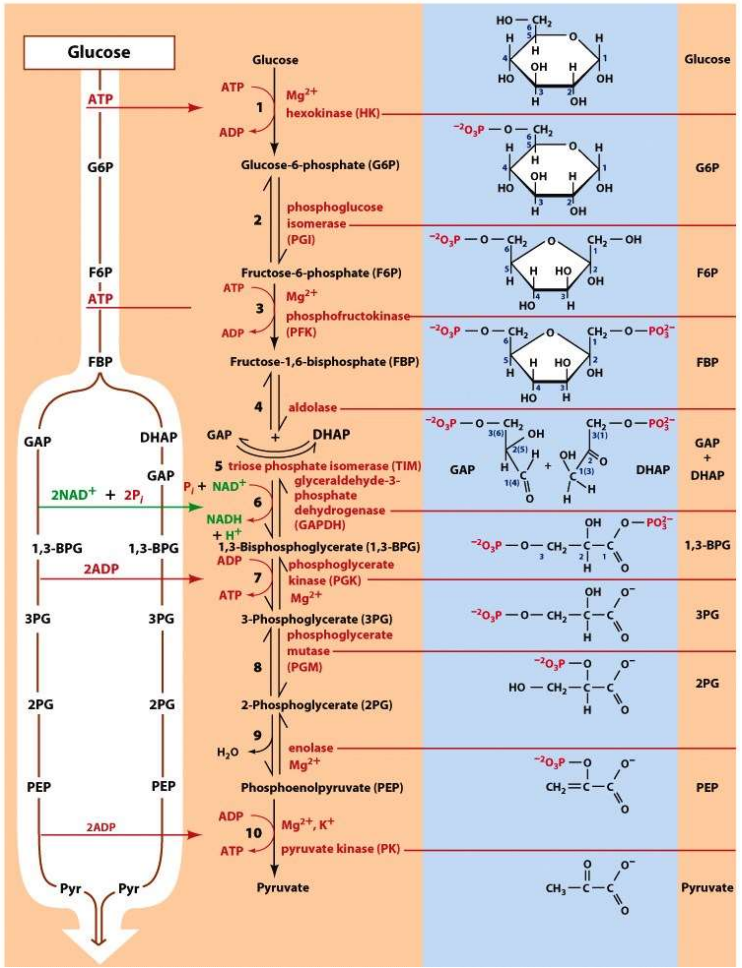
☺ Glycolysis then harvests energy in the form of NADH and ATP

☺ Several steps are irreversible to shift the equilibrium and provide for flux control

☺ Glycolysis provides examples for several basic chemical reactions in metabolism

☺ Fermentation removes NADH under anaerobic conditions

☺ Cancer cells manipulate glycolysis and yeast glycolysis is bistable



Glycogen Metabolism

Voet & Voet, Chapter 18

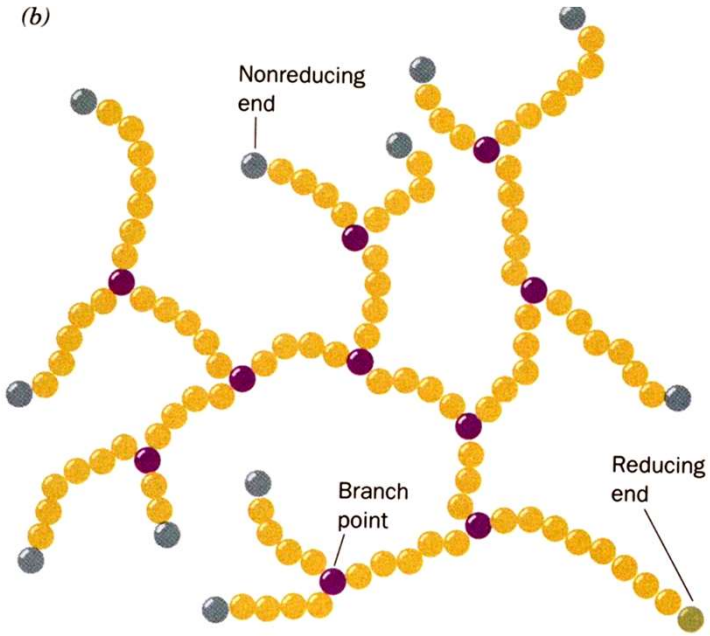
Albert Einstein: "Everything should be made as simple as possible but not simpler"

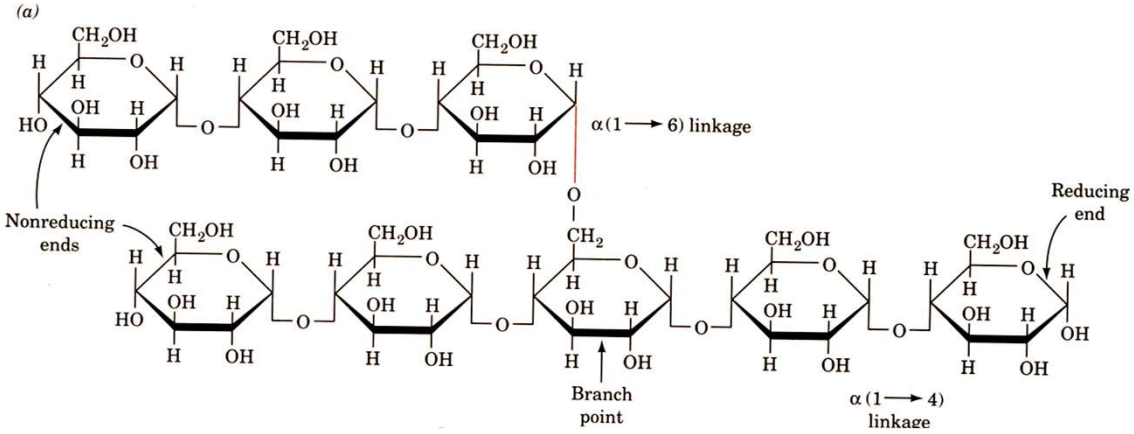
- **Glucose = important fuel (glycolysis, citric aid cycle)**

⇒ needs to be stored to be "ready" for metabolic need

better than fat: rapidly mobilized; can replenish blood glucose; anaerobically metabolized

→ single (BIG) molecules!





- **branches every 8-12 residues**

⇒ fast release at every end!