

A FESTSCHRIFT SYMPOSIUM HONORING REIN SARAL MD

Signaling and Targeting of Cancer Metabolism



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11/15/14

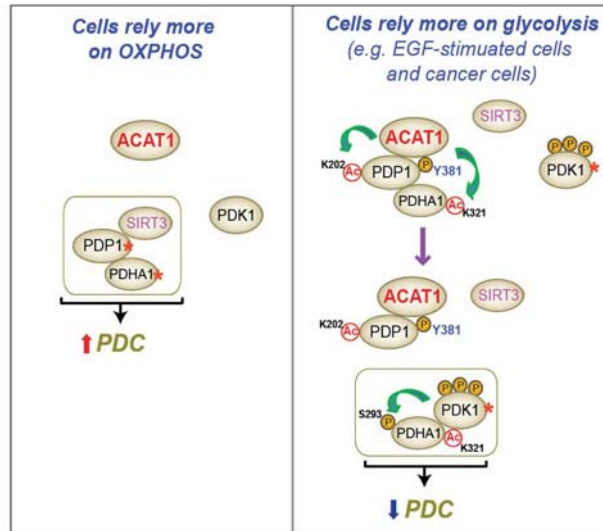
The Warburg effect: a phenomenon of cancer cell metabolism yet poorly understood

- The Warburg effect in cancer cells consists of an increase in aerobic glycolysis and enhanced lactate production.
- Aerobic glycolysis provides not only ATP but also glycolytic intermediates as precursors for anabolic biosynthesis.
- Interestingly, leukemia cells are also highly glycolytic, despite residing within the bloodstream at higher oxygen tensions than cells in most normal tissues.
- Detailed mechanisms underlying the metabolic switch to glycolysis and coordination between glycolysis and anabolic biosynthesis remain unclear.



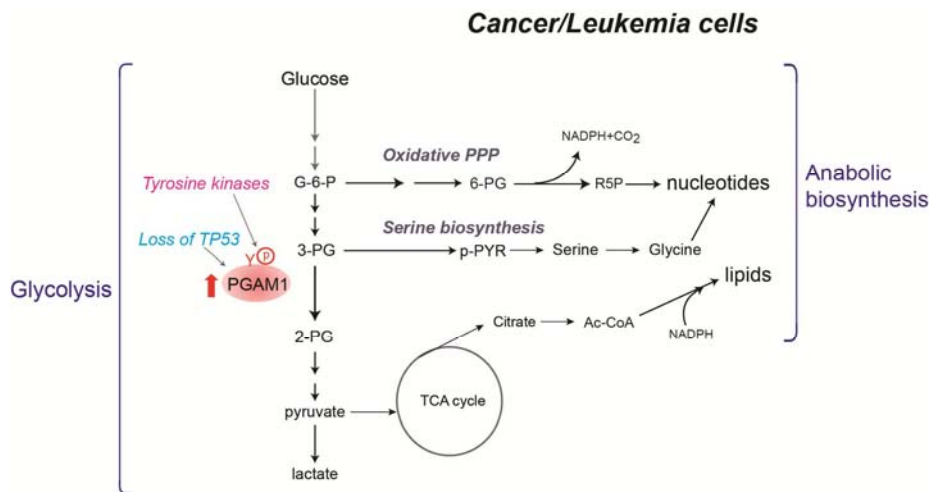
Dr. Otto Warburg (1883-1970)

Tyr-phosphorylation of PDP1 toggles recruitment between ACAT1 and SIRT3 to regulate pyruvate dehydrogenase complex



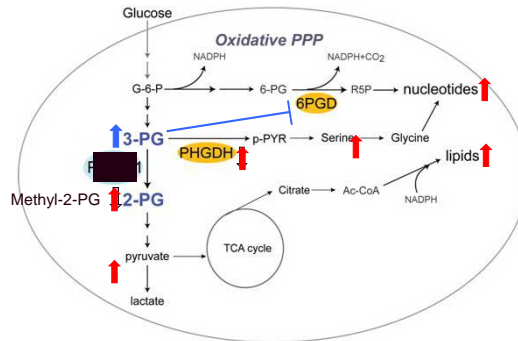
Fan, Shan and Kang et al. (2014) *Molecular Cell*

Phosphoglycerate mutase 1 (PGAM1) is located at the “branching point” between glycolysis and anabolic biosynthesis



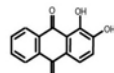
Hitosugi, Zhou et al, 2012, *Cancer Cell*
 Hitosugi, Zhou et al, 2013, *Nature Communications*

PGAM1 controls its substrate 3-PG and product 2-PG to coordinate glycolysis and anabolic biosynthesis

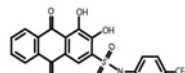


3-PG and 2-PG function as “signaling molecules” to coordinate glycolysis and biosynthesis

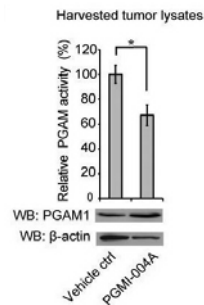
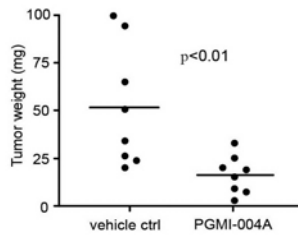
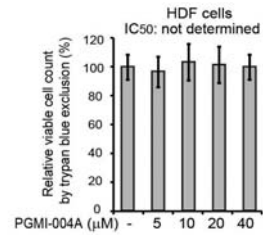
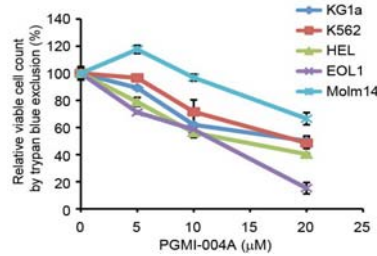
PGAM1 inhibitor PGMI-004A attenuates cancer/leukemia cell proliferation and tumor growth



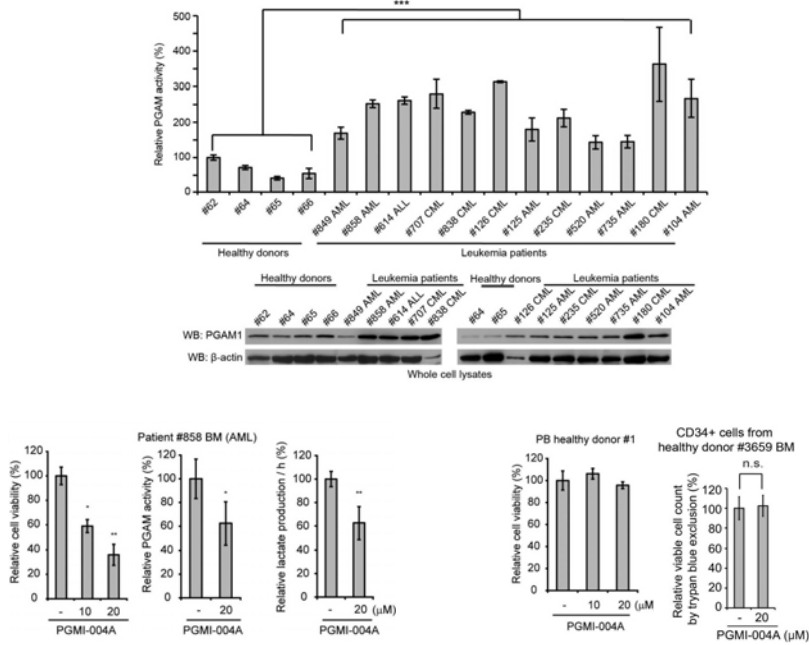
Alizarin



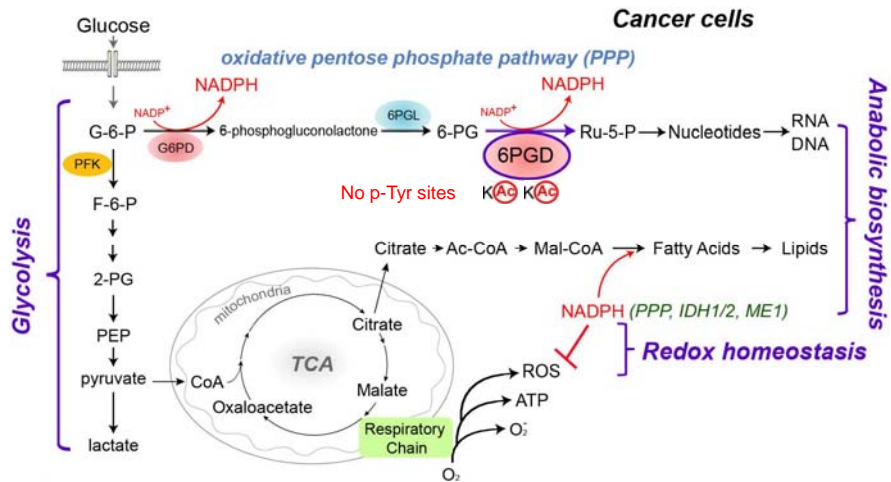
PGMI-004A



PGAM1 is commonly upregulated in human leukemias and represents a promising anti-leukemia target

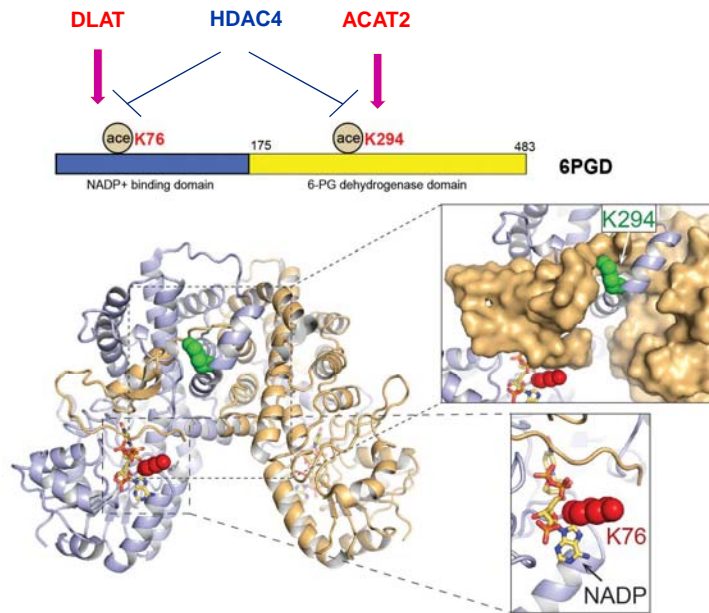


Is 6PGD important for cancer metabolism and tumor growth?

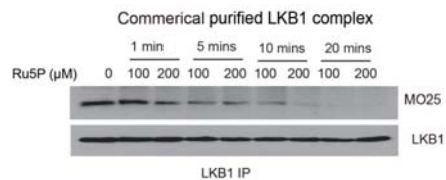
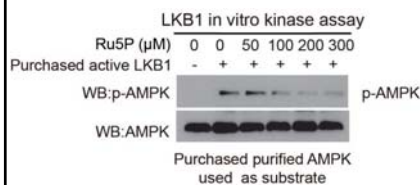
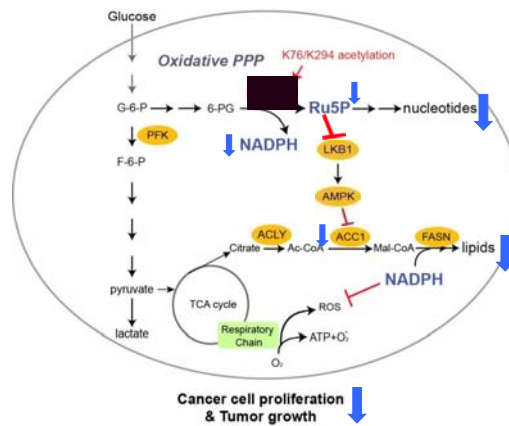


Shan and Elf et al. (2014) *Molecular Cell*
Shan, Elf and Kang et al. (2014) *Nature Cell Biology* (final revision)

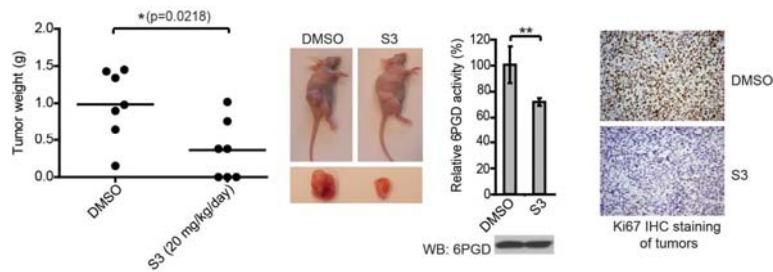
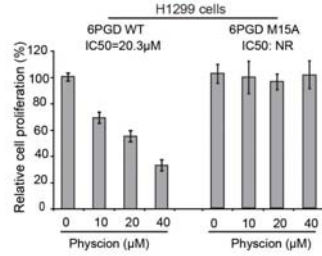
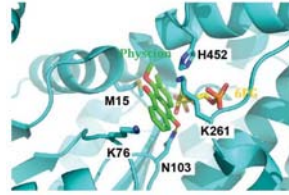
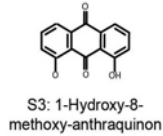
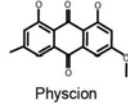
K76 and K294 acetylation activates 6PGD by promoting NADP+ binding and active dimer formation, respectively



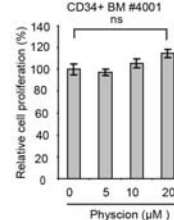
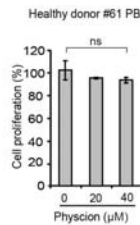
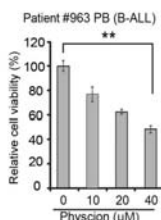
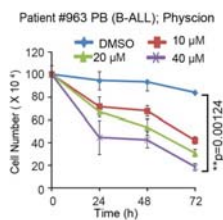
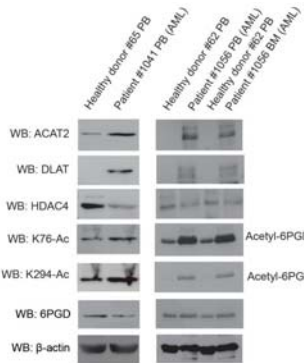
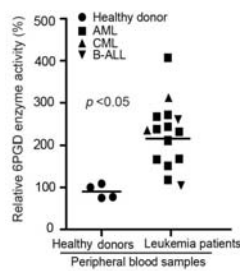
6PGD links PPP and lipogenesis by controlling its product Ru-5-P that disrupts active LKB1 complex



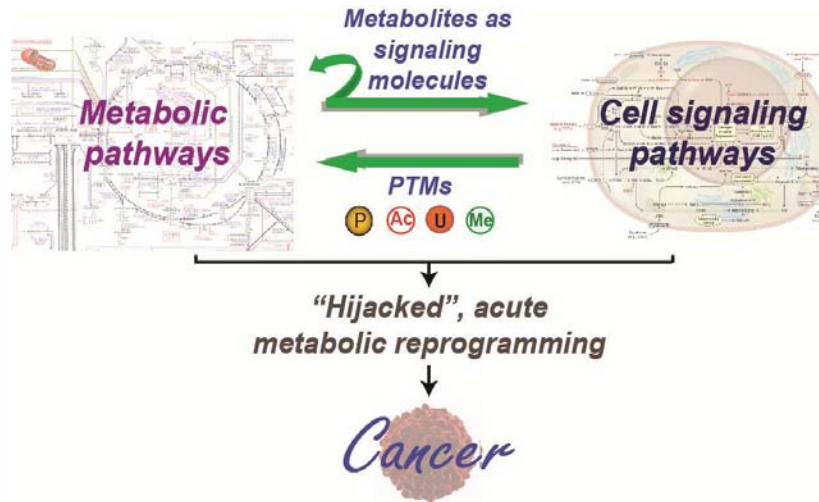
6PGD inhibitors (Physcion and its derivative S3) inhibit cancer cell proliferation and tumor growth



6PGD is upregulated in human leukemias and represents a promising anti-leukemia target



“Acute” metabolic reprogramming in cancer cells



Acknowledgements

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