HepG2 cells: Unreliable for gluconeogenesis research ?

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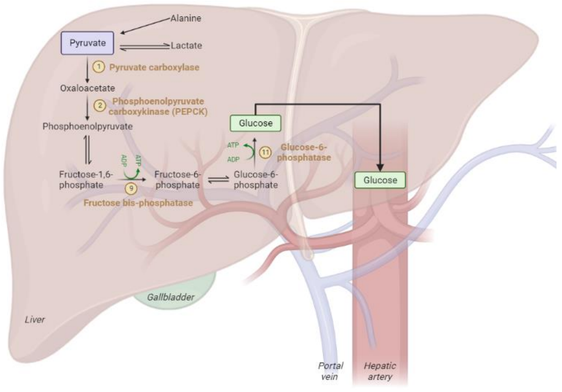
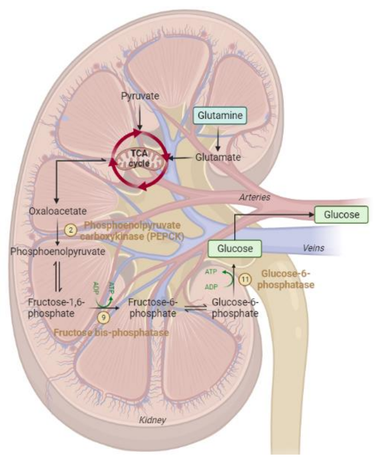
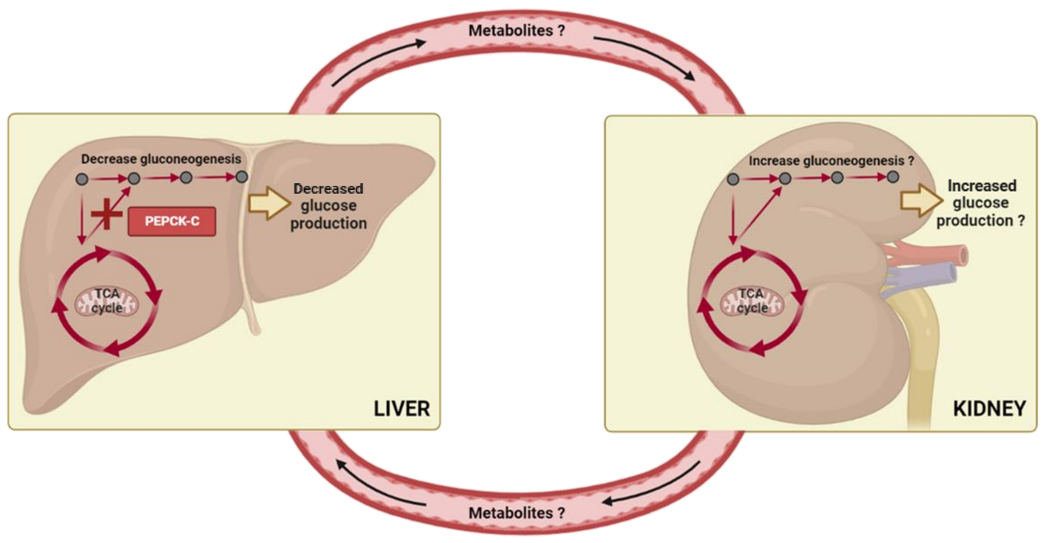
GLUCONEOGENESIS

Every cell in the human body needs energy to sustain its metabolic functions. Glucose regulation is essential, especially the gluconeogenesis pathway. During fasting and stress conditions, hepatic gluconeogenesis has a crucial role to maintain glucose homeostasis. However, renal gluconeogenesis may also account for 40% of systemic gluconeogenesis.

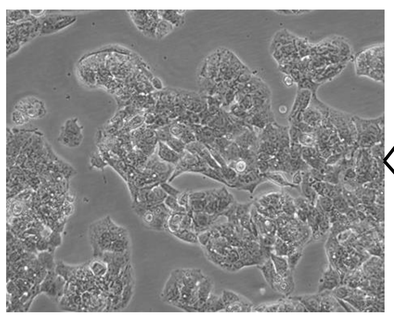




LIVER-KIDNEY CROSSTALK

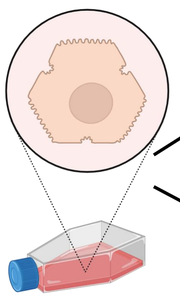


IN VITRO MODEL: HepG2 CELLS



- Easy to use & maintain
- Widely used in research

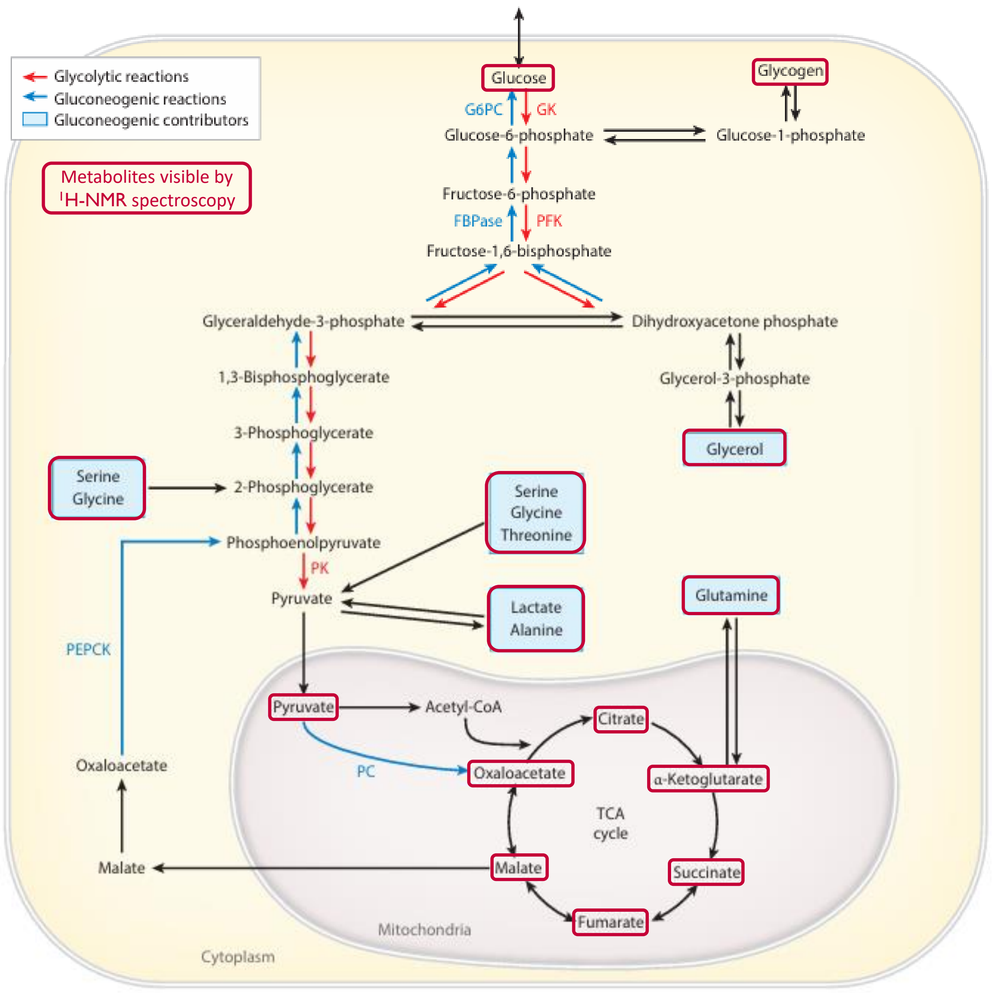
M&M



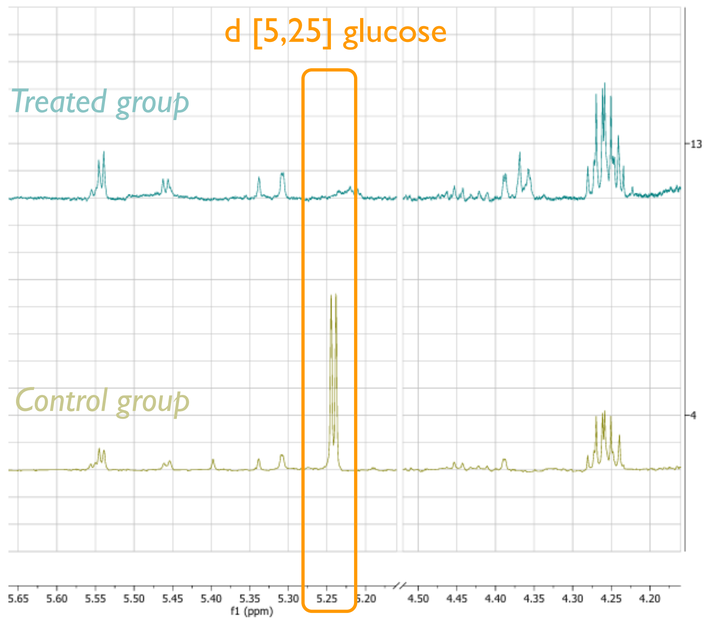
Glucose medium 5mM + 10% FBS — 24h
Control group

Glucose- and FBS-free medium — 16h — 8h
Gluconeogenesis stimulation
20mM lactate, 2mM pyruvate — 500nM Dexamethasone, 100µM cAMP

PROTON NUCLEAR MAGNETIC RESONANCE



Gluconeogenesis pathway



Metabolite	Chemical shift	T vs CTRL Polar phase	T vs CTRL ECM
Lactate	1,32 [d] / 4,16 [q]	↑	
Glycine	3,56 [s]	↑	
Glutamate	2,36 [m]/ 2,5 [m]	↑	
Leucine	0,96 [t]/ 0,97 [t]	↑	↑
Isoleucine	0,94 [t]/ 1,01 [d]	↑	↑
Valine	0,99 [d]/ 1,04 [d]	↑	↑
Ketoisoleucine	0,88 [d]/ 1,09 [d]		↑
Lysine	1,48 [m]/ 1,73 [m]/ 1,91 [m]/ 3,03 [t]/ 3,76 [t]		↑
Alanine	1,48 [d]/ 3,79 [q]		↑
α-Ketoglutarate	2,45 [t]/ 3,01 [t]		↑
Threonine	1,34 [d]/ 3,59 [d]/ 4,26 [ABX]		↑
Glucose	3,24 [dd]/ 3,4 [t]/ 3,47 [ddd]/ 3,49 [t]/ 3,72 [dd]/ 3,9 [dd]/ 4,64 [d]/ 5,2 [d]		↓

~~Glucose~~ in the extracellular medium

~~Gluconeogenesis~~ activity under stimulation

CONCLUSION

HepG2 cell line does not seem like a reliable ally to study gluconeogenesis → another model is needed

→ Primary hepatocytes could represent a valuable alternative coupled with MS-based metabolomic instead of NMR due to a limitation in cell number

References :Zhang X, Yang S, Chen J, Su Z. Unraveling the Regulation of Hepatic Gluconeogenesis. Front Endocrinol (Lausanne). 2019 Jan 24;9:802. Legouis D, Faivre A, Cippà PE, de Seigneux S. Renal gluconeogenesis: an underestimated role of the kidney in systemic glucose metabolism. Nephrology Dialysis Transplantation. 2022 Aug 1;37(8):1417–25.