

Microenvironmental regulation of the hexosamine biosynthesis pathway

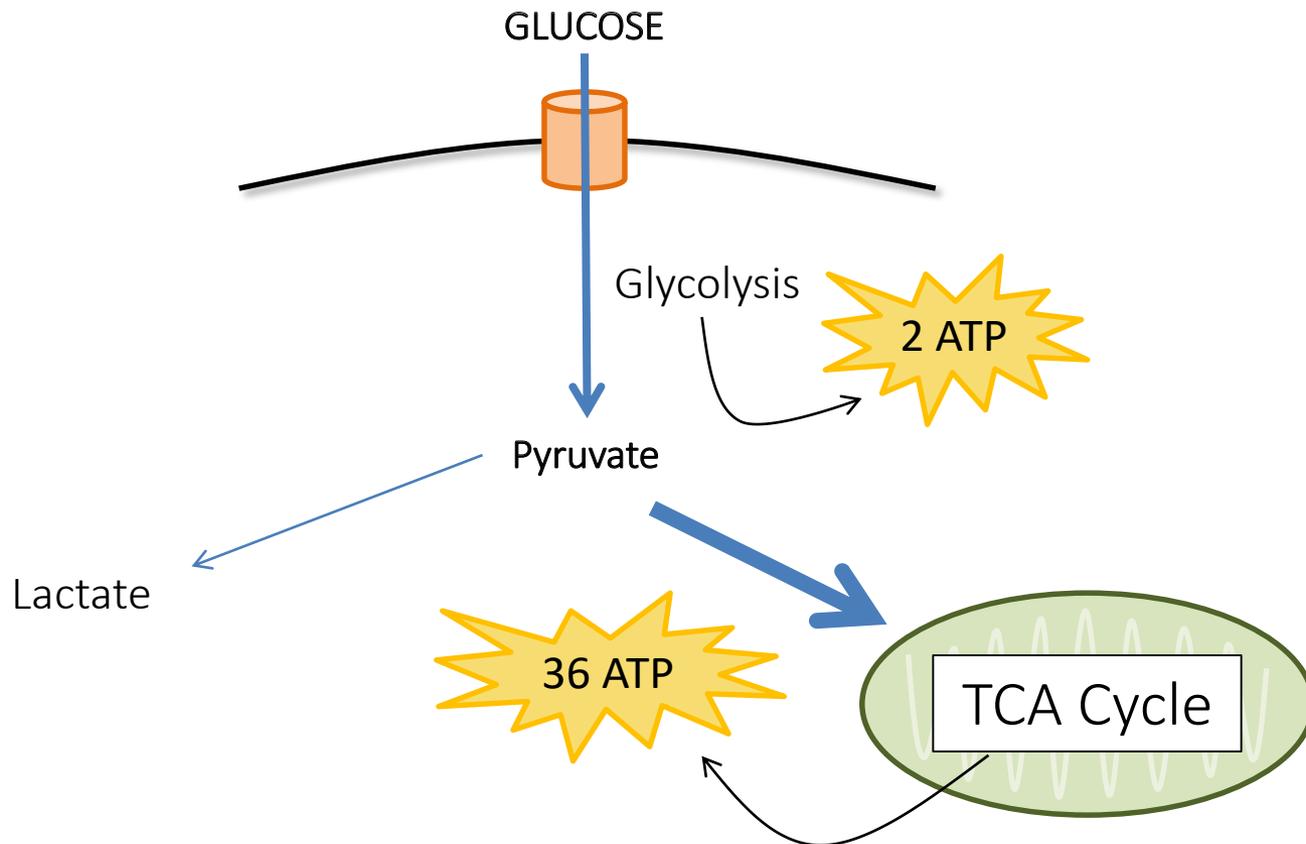
Sydney Campbell

Wellen Lab

Herpesvirus Symposium, 6.23.17

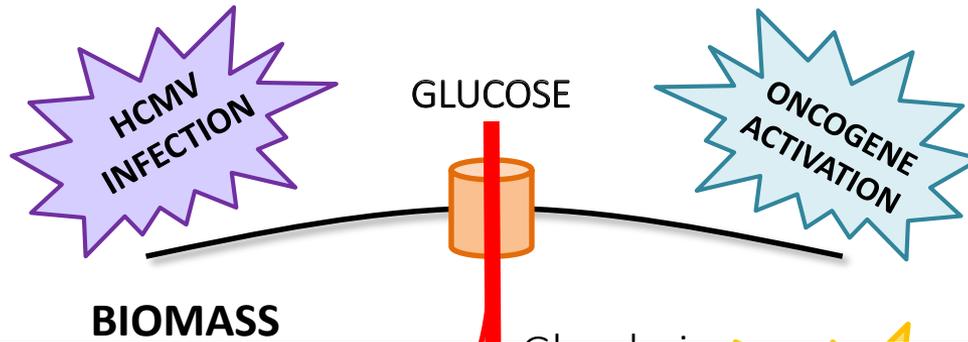
The Warburg effect

Nonproliferating, differentiated tissue

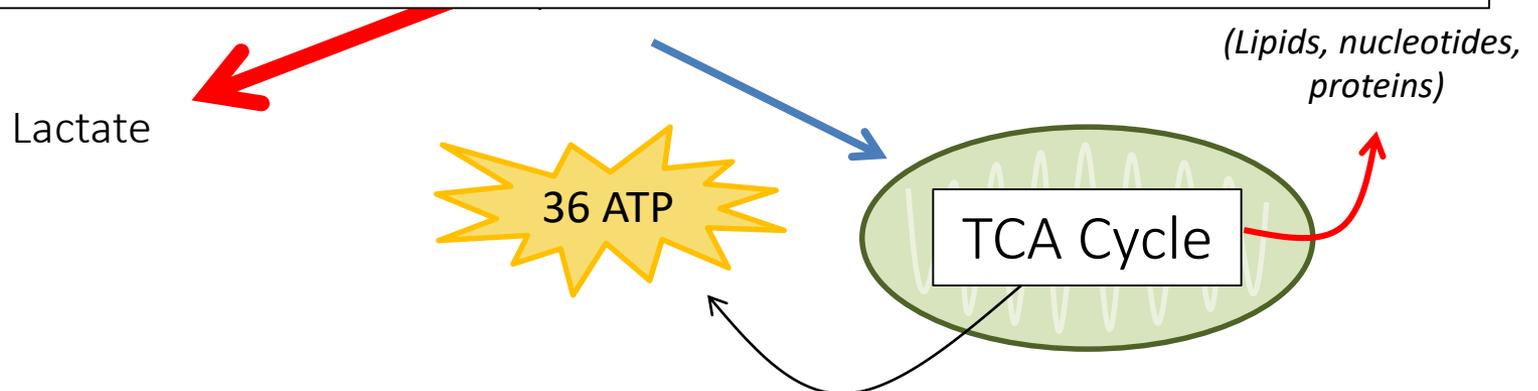


The Warburg effect

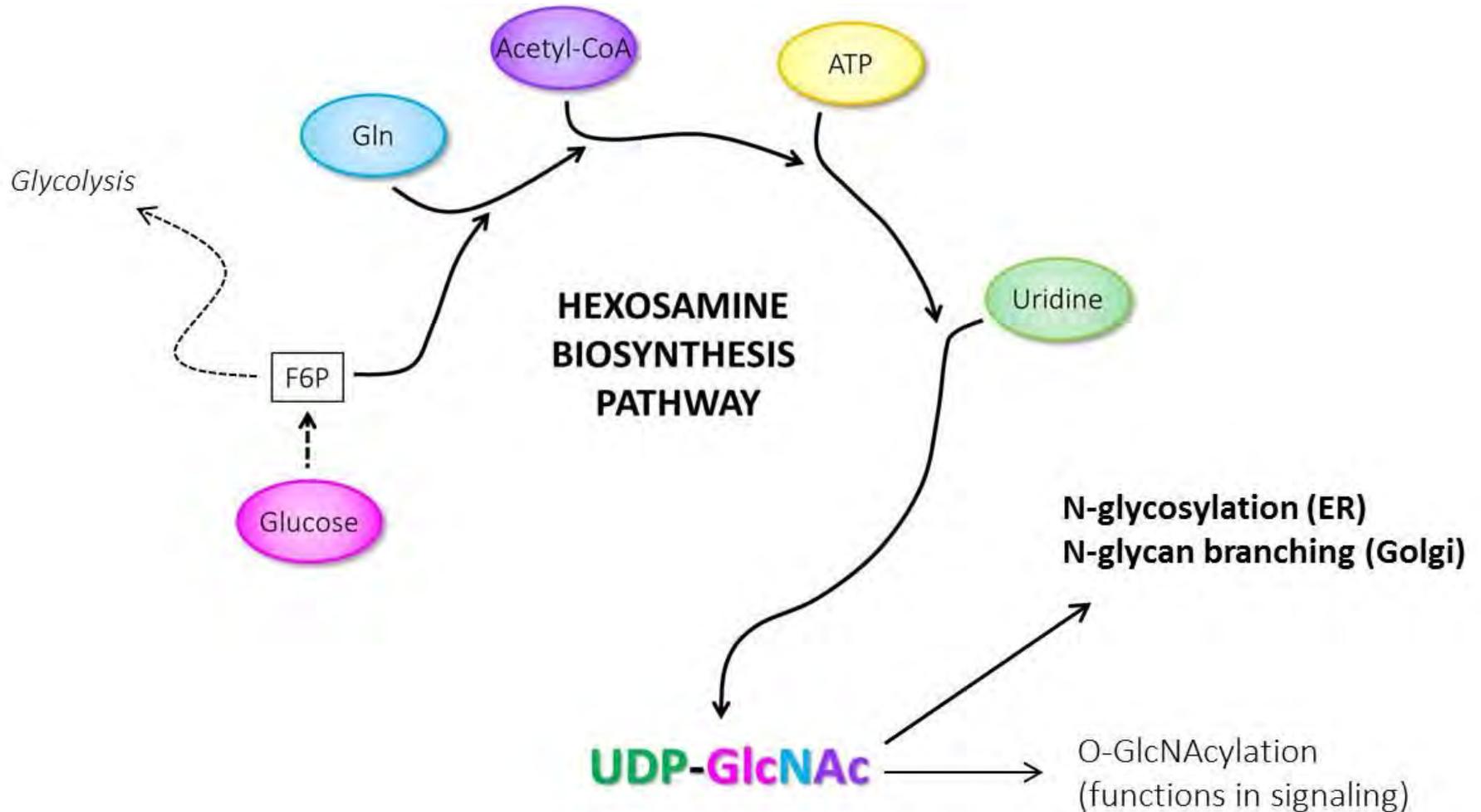
Highly proliferative, tumor, or virus-infected cells



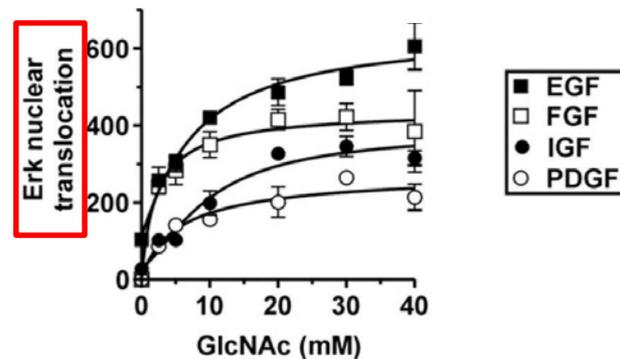
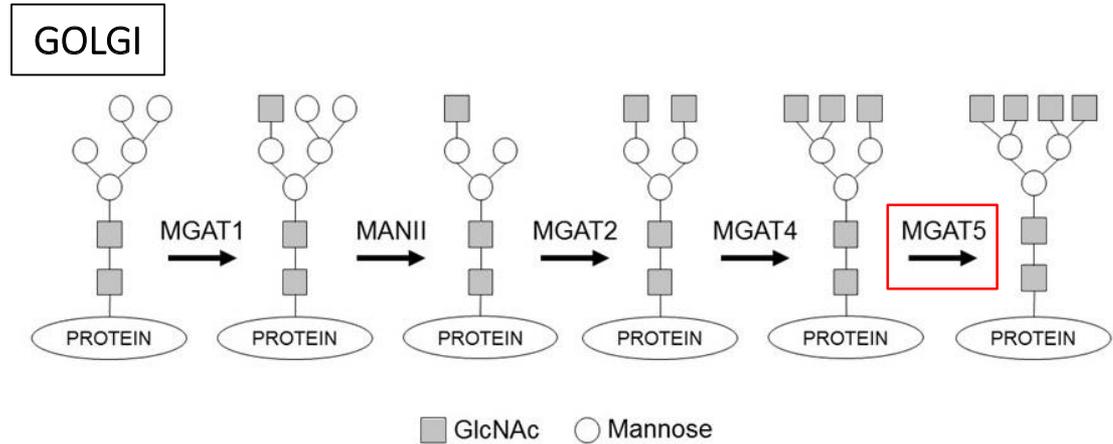
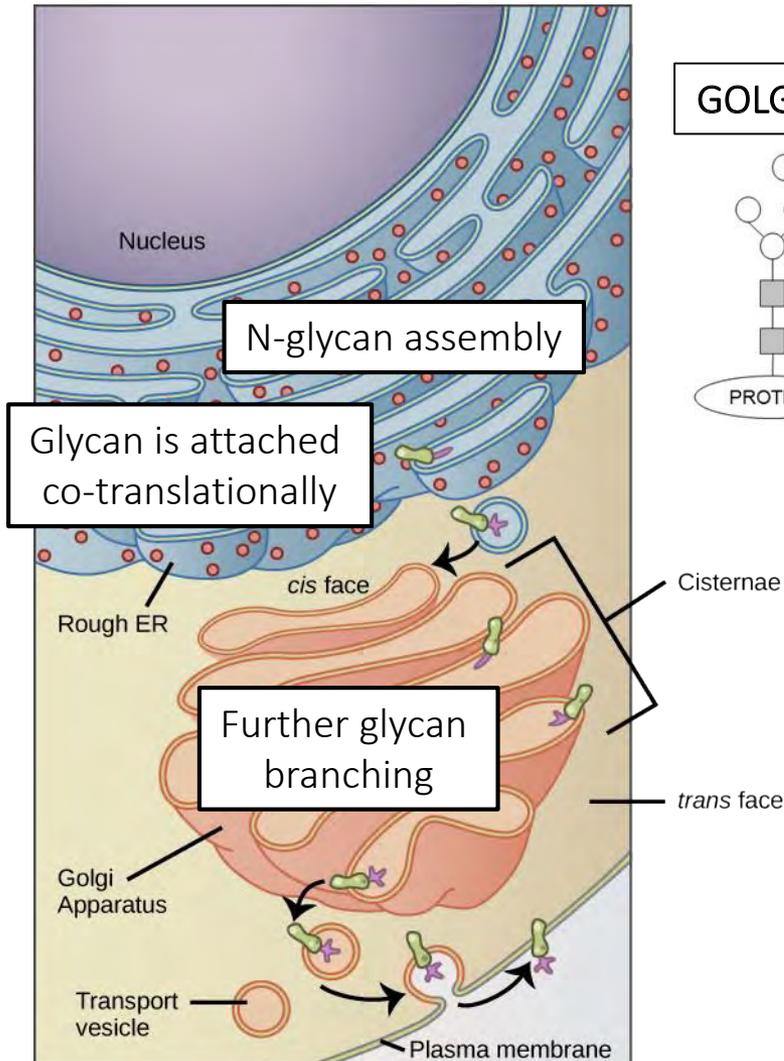
Understanding tumor metabolism can provide insight into metabolic alterations in virus-infected cells.



How do cells sense and interpret their nutritional context?

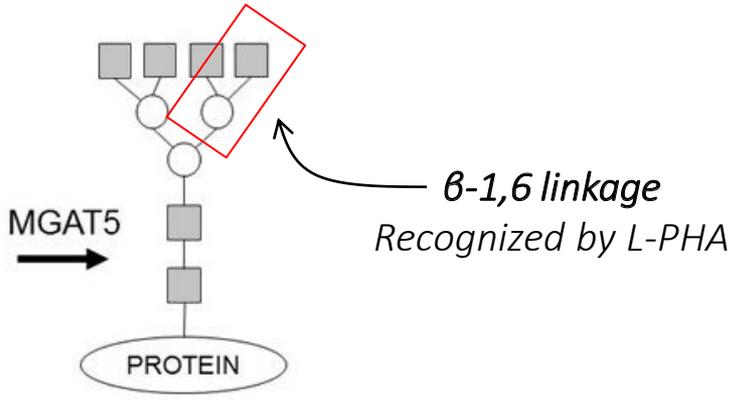
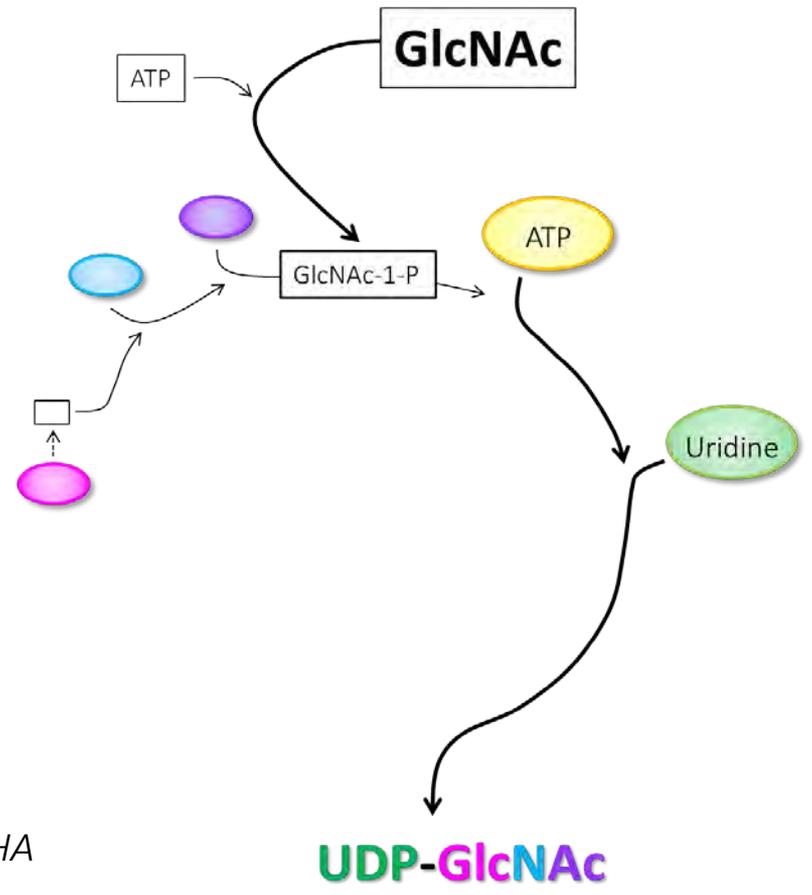
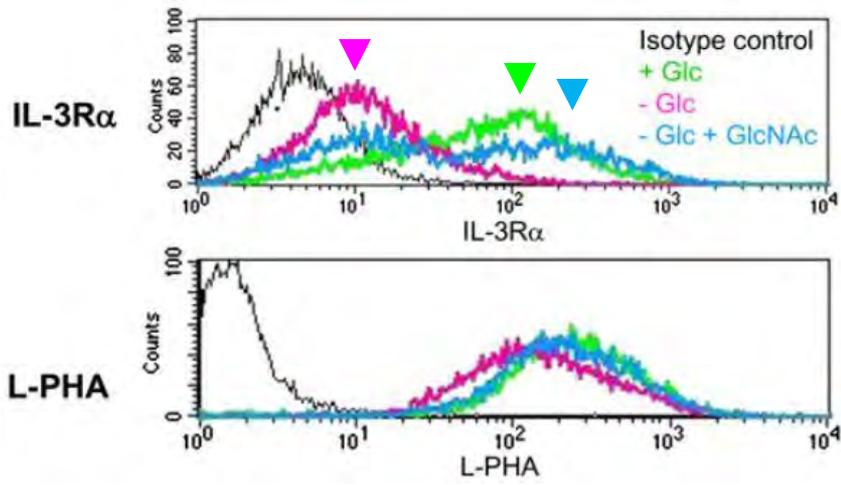


GlcNAc availability can be limiting for N-glycan synthesis

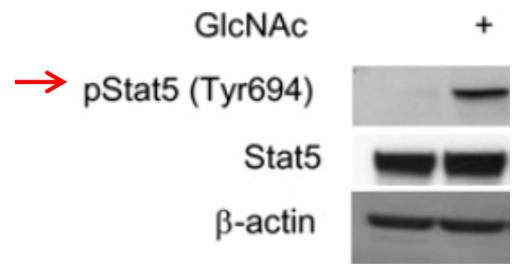
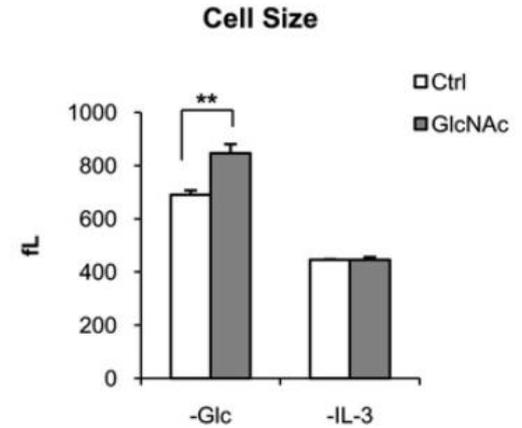
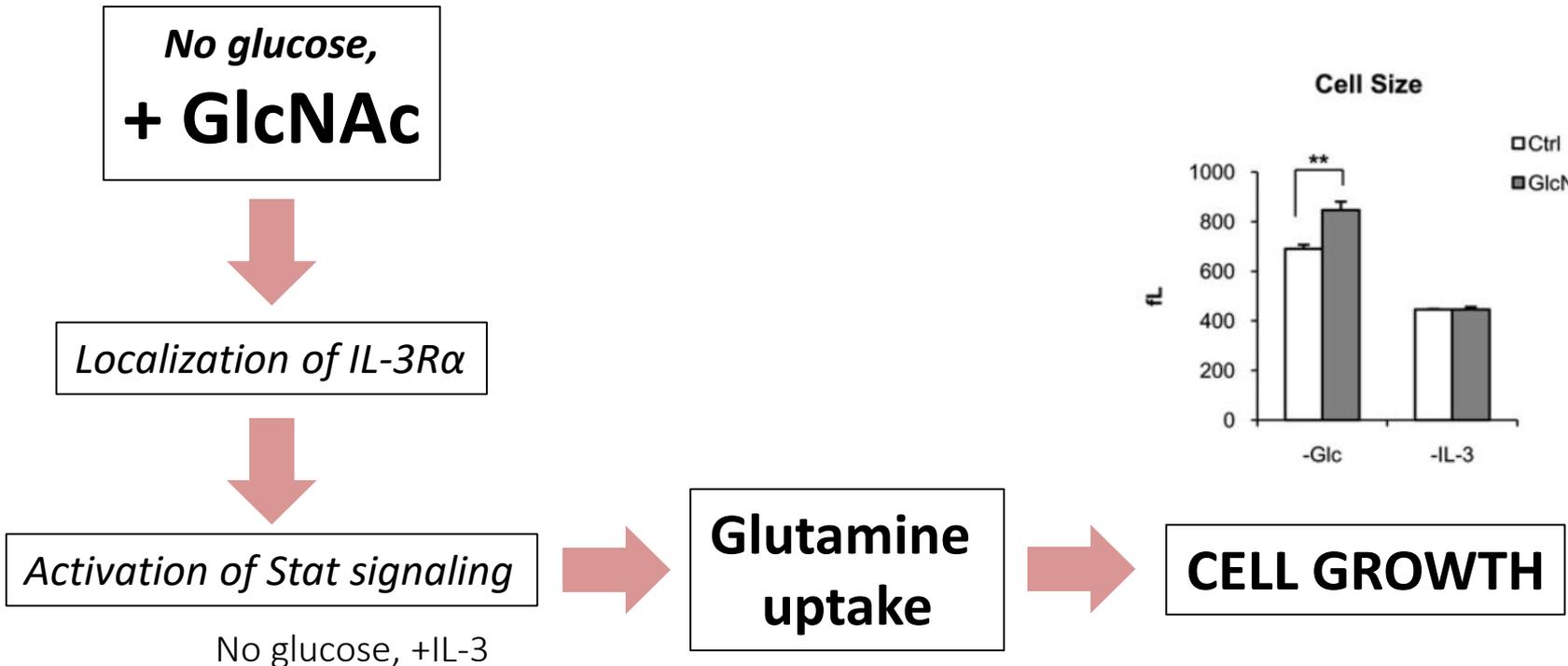


GlcNAc availability impacts localization of specific membrane proteins

IL-3 dependent hematopoietic cells

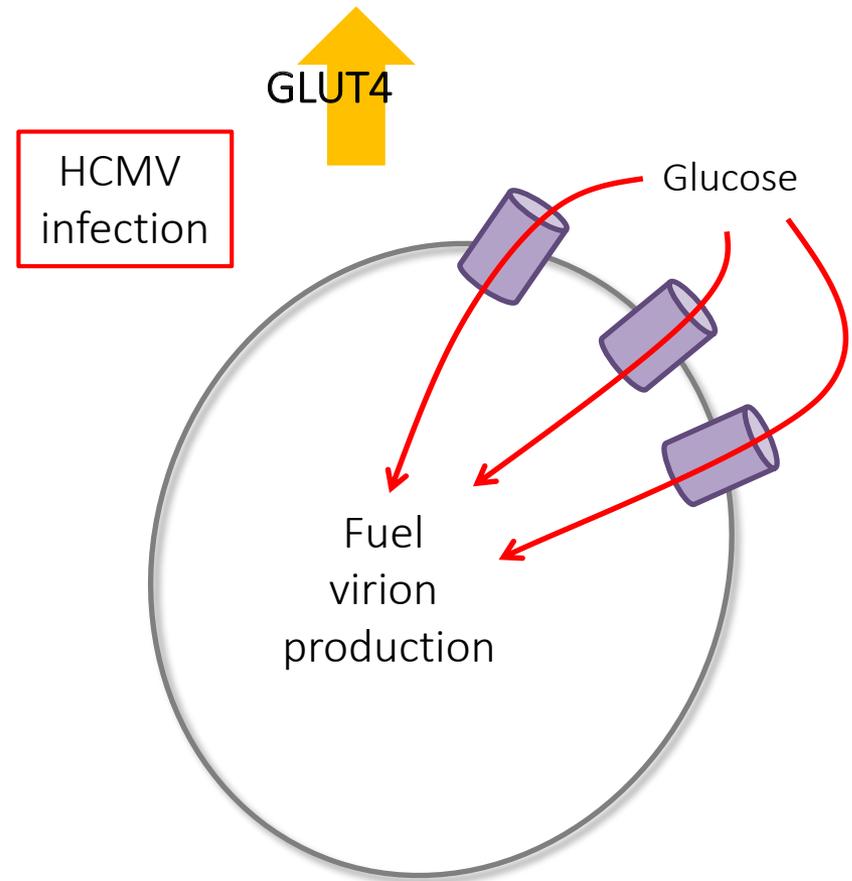


GlcNAc can rescue cell growth in the absence of glucose



Glycoproteins are critical in virus infection and disease

- Enveloped viruses have extensive glycoproteins on their surface
- HCMV infection increases uptake and production of HBP metabolites (*Munger et al, PLoS Pathogens 2006; Yu et al, J. Virology 2010; Chambers et al, J. Virology 2010*)
- O-GlcNAcylation is important for HCMV replication and assembly (*Greis et al, J. Virology 1994; Angelova et al, J. Virology 2015*)

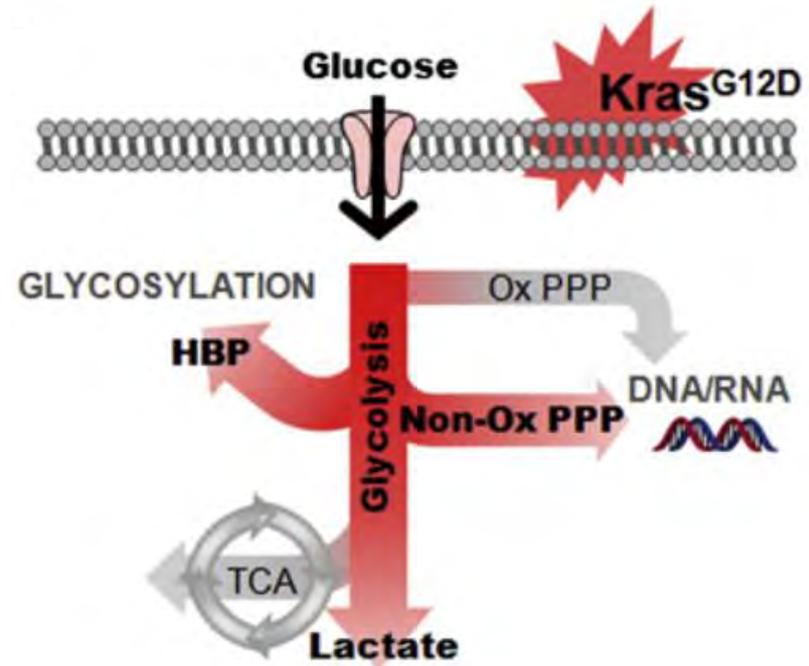


Oncogenic or virus-related reprogramming can increase HBP flux

Nearly 90% of PDAC have a RAS mutation, and in 99% of those it is a KRAS mutation.
(NCI)



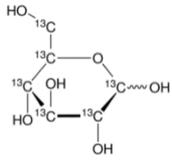
■ KRAS ■ NRAS ■ HRAS



Ying et al, *Cell* 2012

Oncogenic signaling can impact glycan branching

GLUCOSE, U-¹³C



F6P



GlcN6P



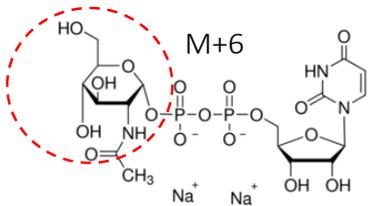
GlcNAc6P



GlcNAc1P

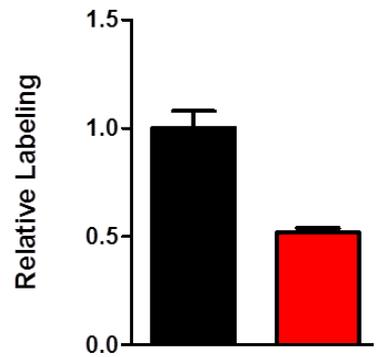


UDP-GlcNAc

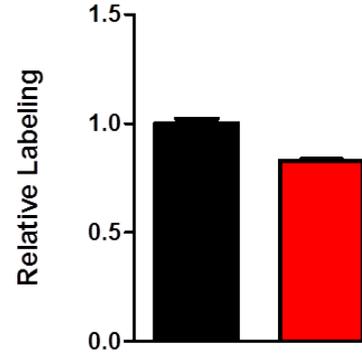


MiaPaCa

GlcNAc-1/6-P



UDP-GlcNAc

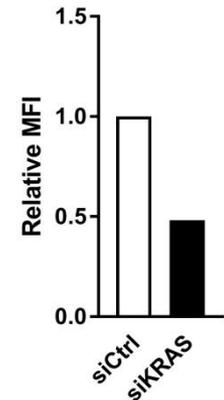


■ DMSO

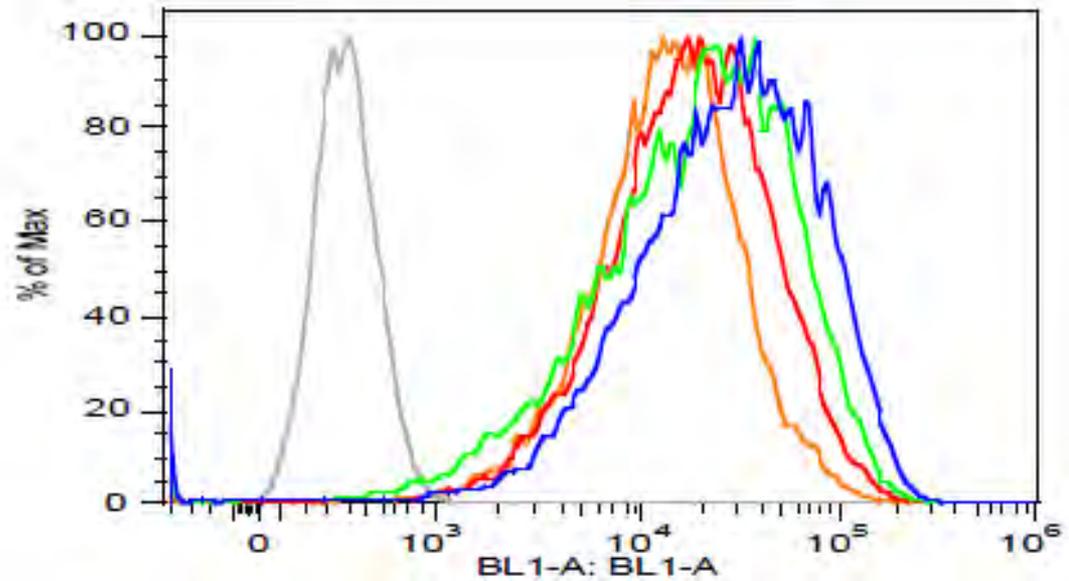
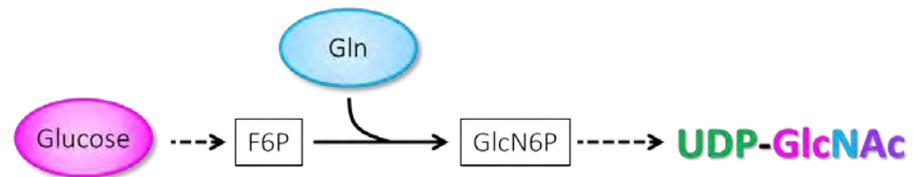
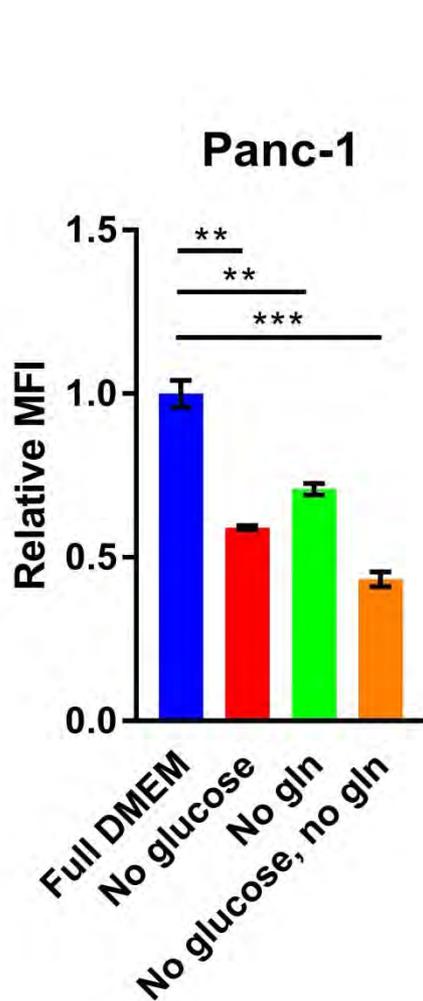
■ 1 uM MEKi

LPHA

MiaPaCa



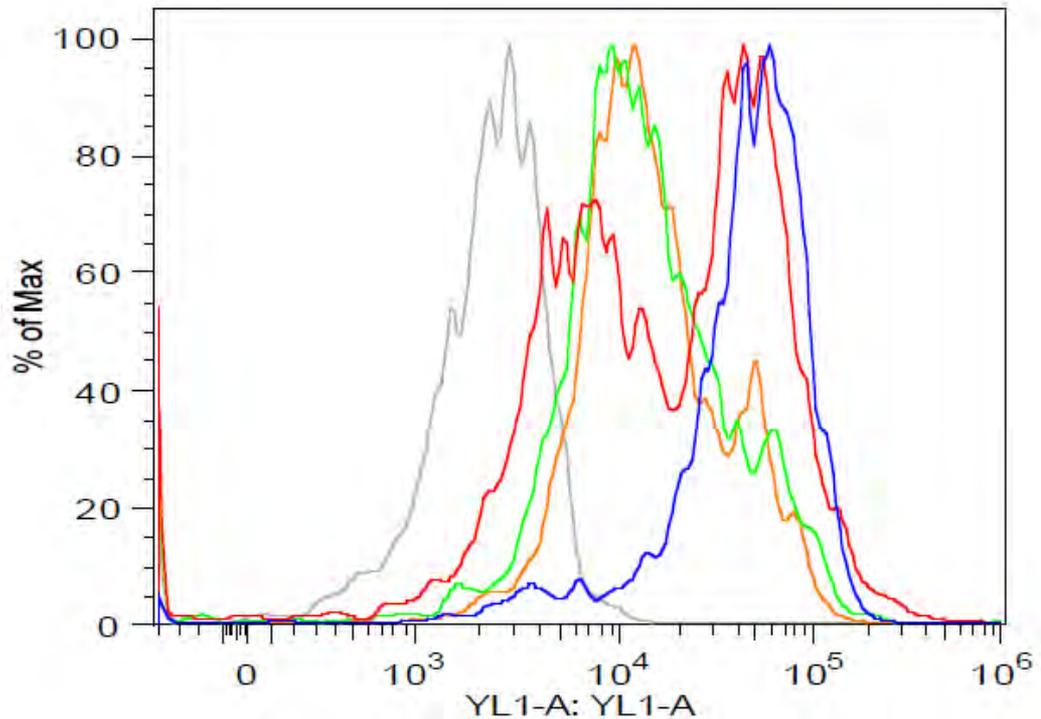
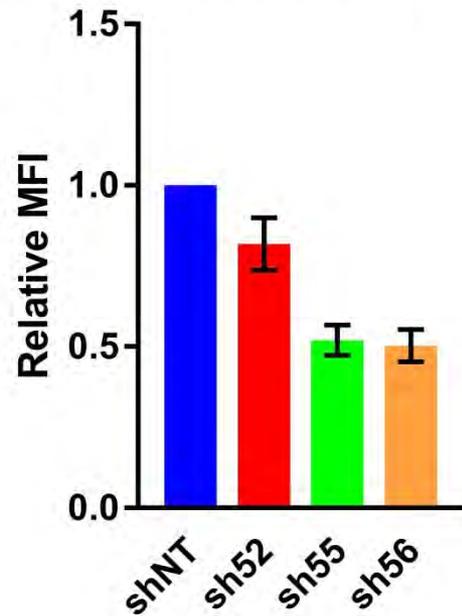
Microenvironment conditions impact N-glycan branching



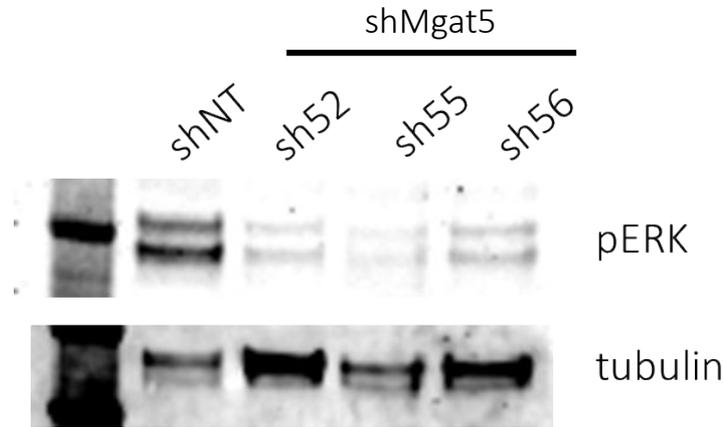
Mgat5 knockdown decreases glycan branching

Mouse PDAC cells

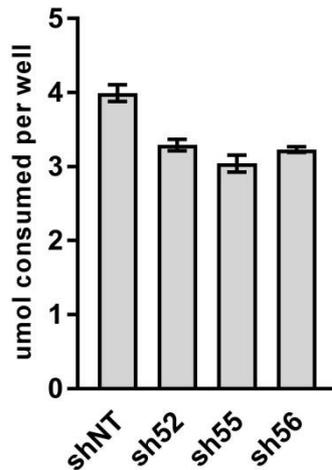
MH2838, shMgat5



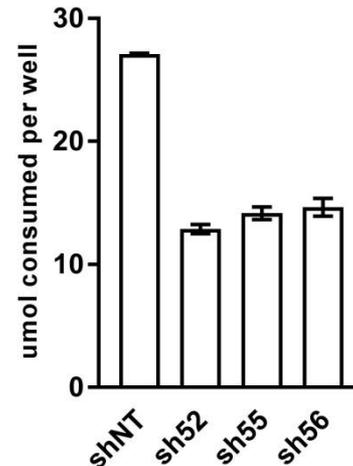
Mgat5 silencing leads to suppression of ERK phosphorylation and nutrient uptake



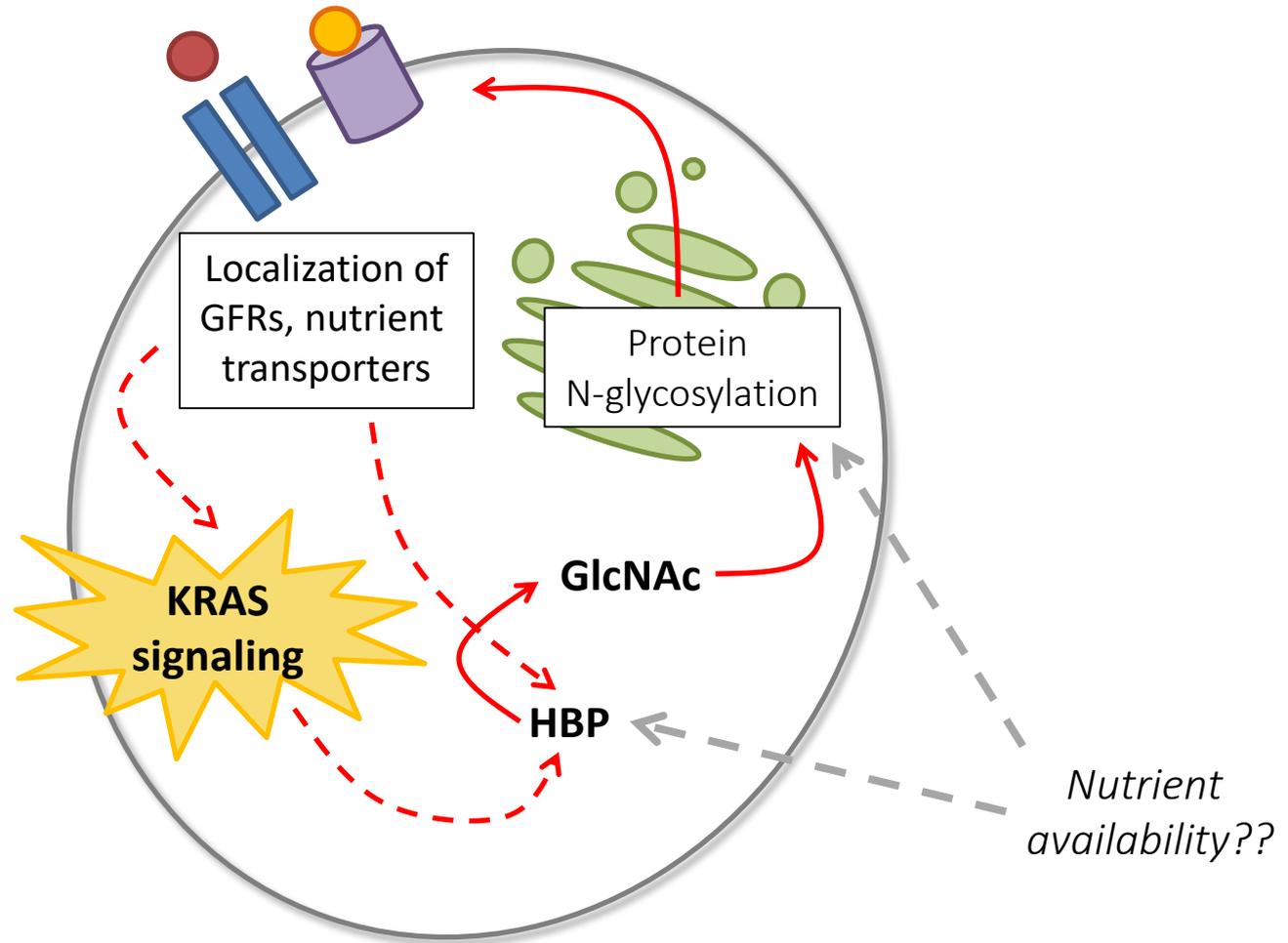
Glutamine consumed, MH2838



Glucose consumed, MH2838



Working model



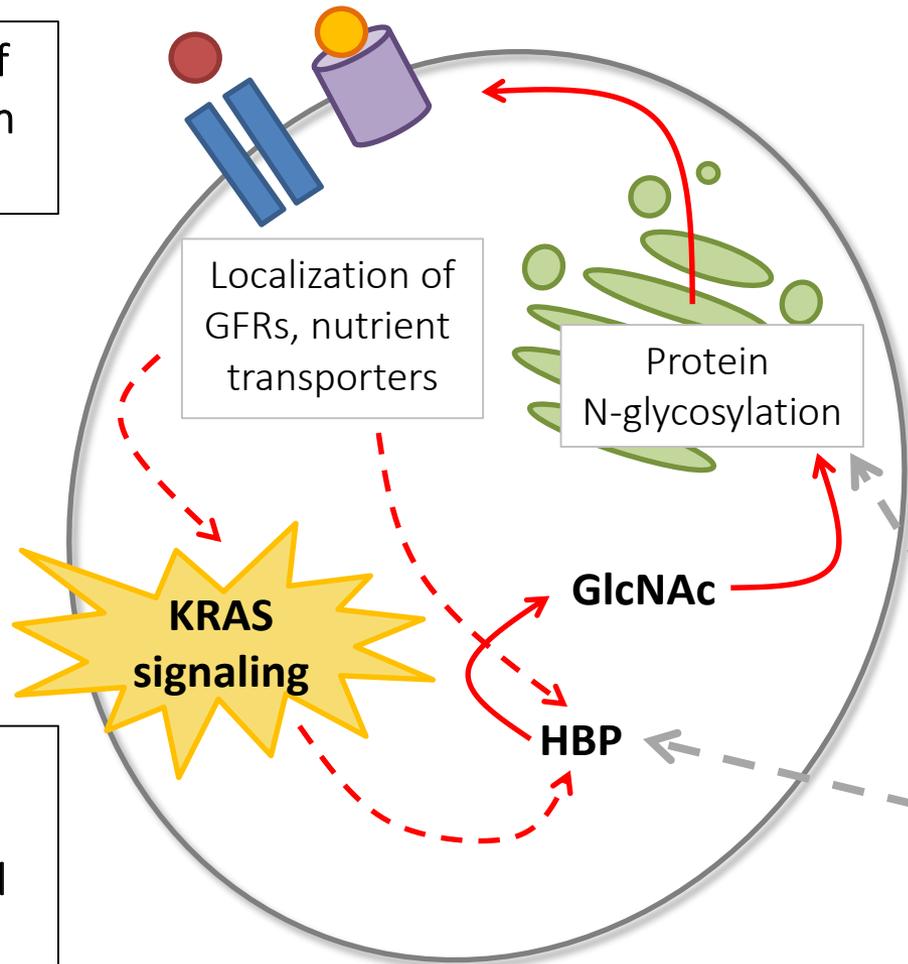
Next questions

What is the role of glycan branching in nutrient uptake ?

Localization of GFRs, nutrient transporters

Protein N-glycosylation

What membrane proteins are impacted by Mgat5 knockdown?



How does glycan branching impact tumor growth and metastasis?

Nutrient availability??

Thank you!

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