metabolic reprogramming - a hallmark of oncogenic viruses

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TARGETS OF IMMUNOTHERAPY OF CHRONIC VIRAL INFECTIONS AND CANCER
Rīga Stradiņš University
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30 to 40% of all cancer have a viral etiology

Oncovirus	Cancer types
Human Papillomavirus	All cervical cancers Majority of anal and vaginal carcinomas Cancers of the oral cavity and pharynx
Adenovirus	Oncogenic in rodents but not humans Transforming capacity in vitro
Hepatitis B virus	Hepatocellular carcinoma
Hepatitis C virus	Hepatocellular carcinoma Non-Hodgkin lymphoma
Epstein-Barr virus	Burkitt, Hodgkin lymphoma T-cell / NK-cell lymphomas Nasopharyngeal and gastric carcinomas
Kaposi's Sarcoma-associated Herpes Virus	Kaposi sarcoma Primary effusion lymphoma
Human Cytomegalovirus	'Oncomodulator'
Human T-cell lymphotropic virus type 1	Adult T-cell leukemia and lymphoma

Oncoviruses are necessary but not sufficent for cancer development:

Prevalence of virus in the population **> >** **Cancer incidence**

How do Oncoviruses contribute to cancer ?

Integrations that activate/inactivate oncogenes or tumor suppressors

Expression, stabilisation, degradation of tumor suppressors /oncogenes or cellular factors that drive key signal transduction pathways

Chronic cellular stress and activation of inflammatory responses

Multi hit model of carcinogenesis

Most virally-induced cancers emerge in the context of persistent infections

- Avoid apoptosis (p53, Bcl2)
- Modulate and evade immune responses (Pd1)
- Stimulate growth and proliferation (pRB, E2F1, etc)
- Induction of vascularization (HIF1a)
- Induction of cell migration

→ Viruses and cancer cells share similar needs

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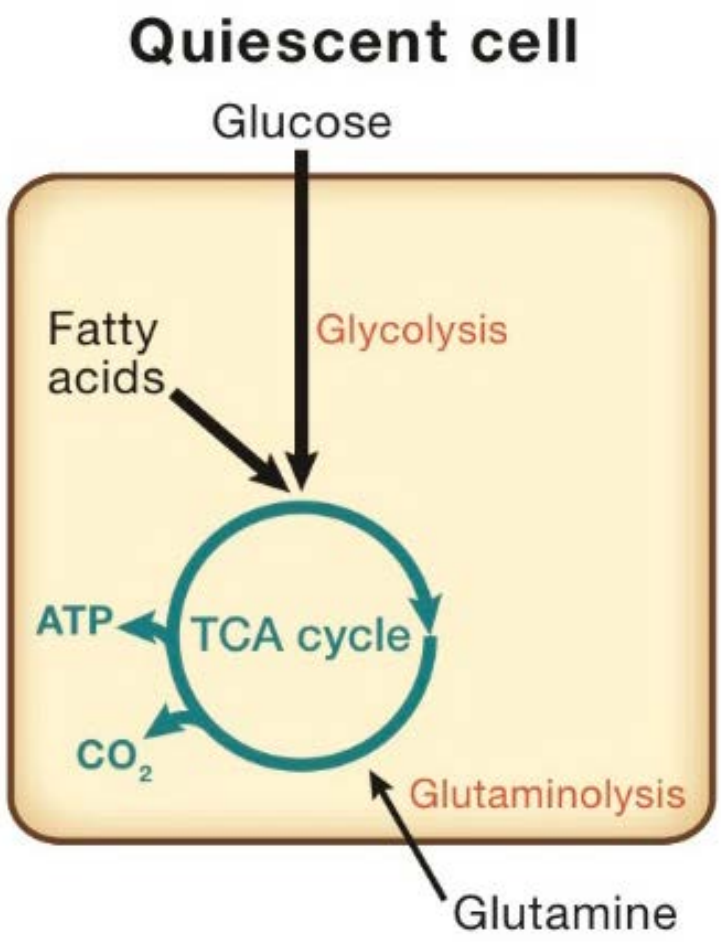
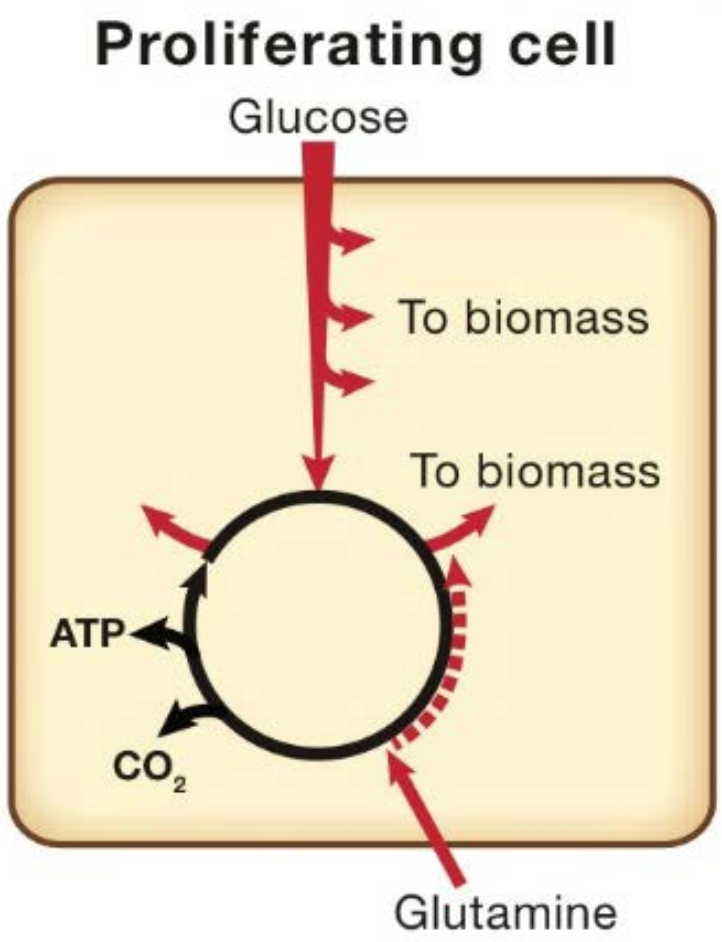
→ Viruses and cancer cells share similar needs

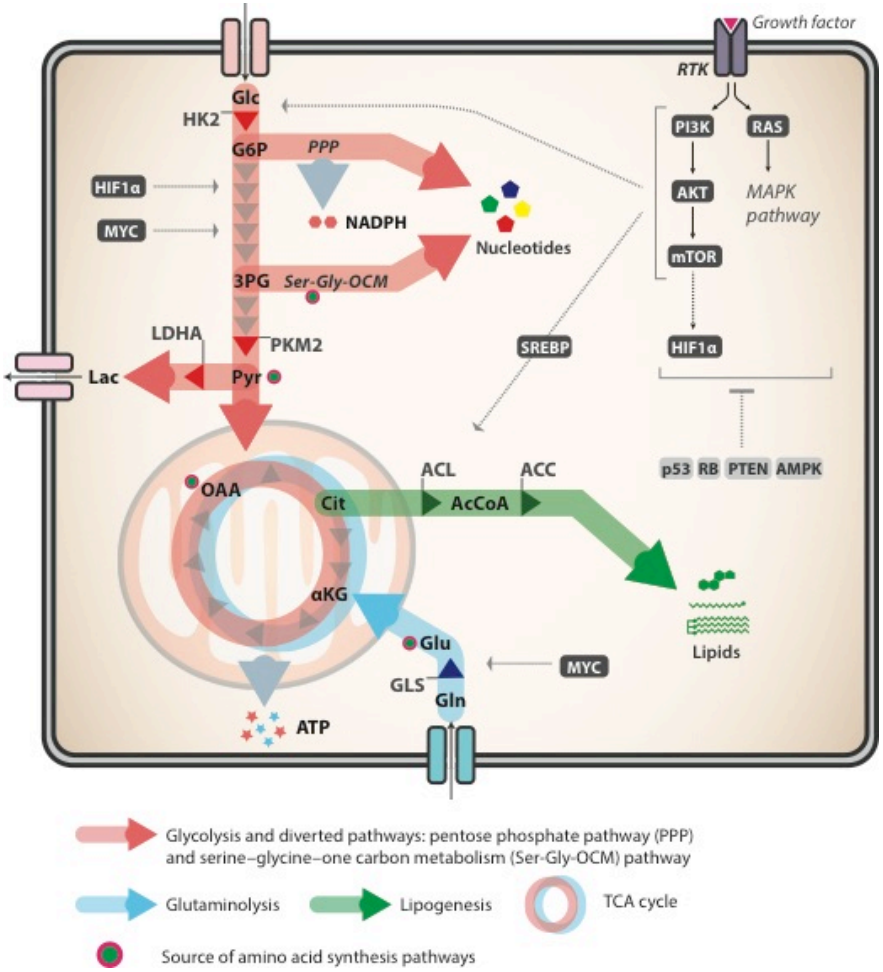
Viruses need biomass for **virion production**

Tumor cells need biomass for **cell division**





Key metabolic enzymes and pathways that are targeted by oncogenic viruses



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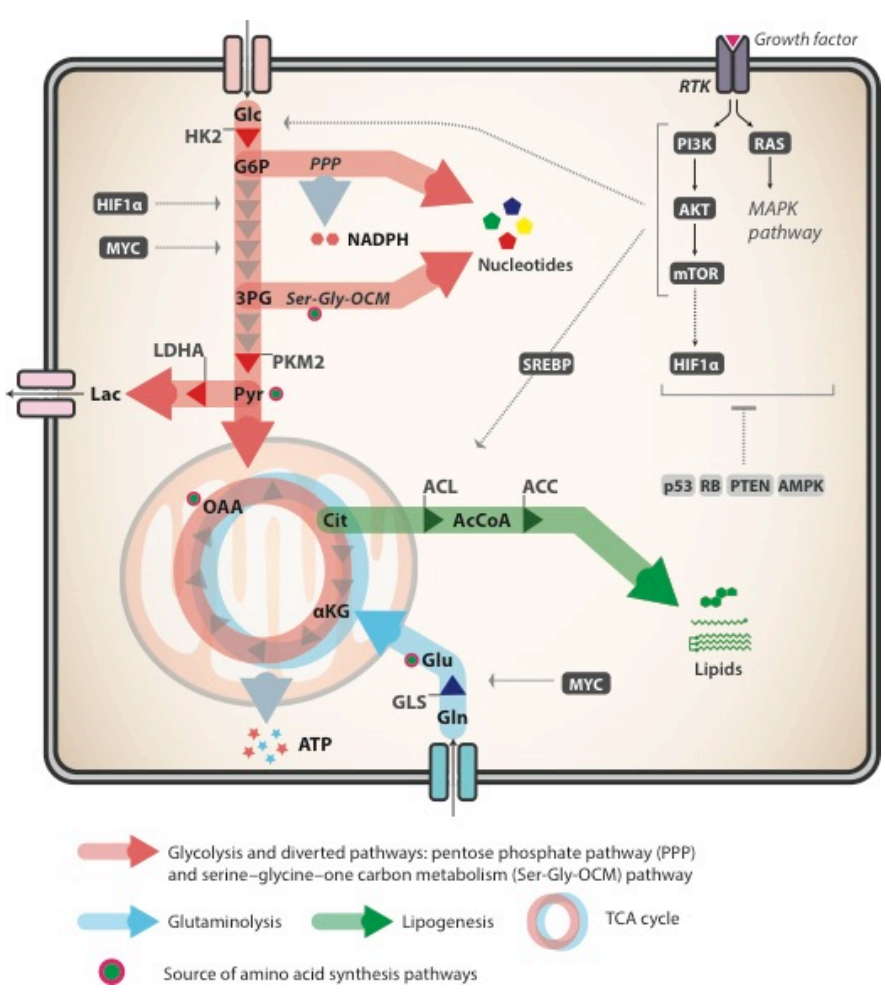
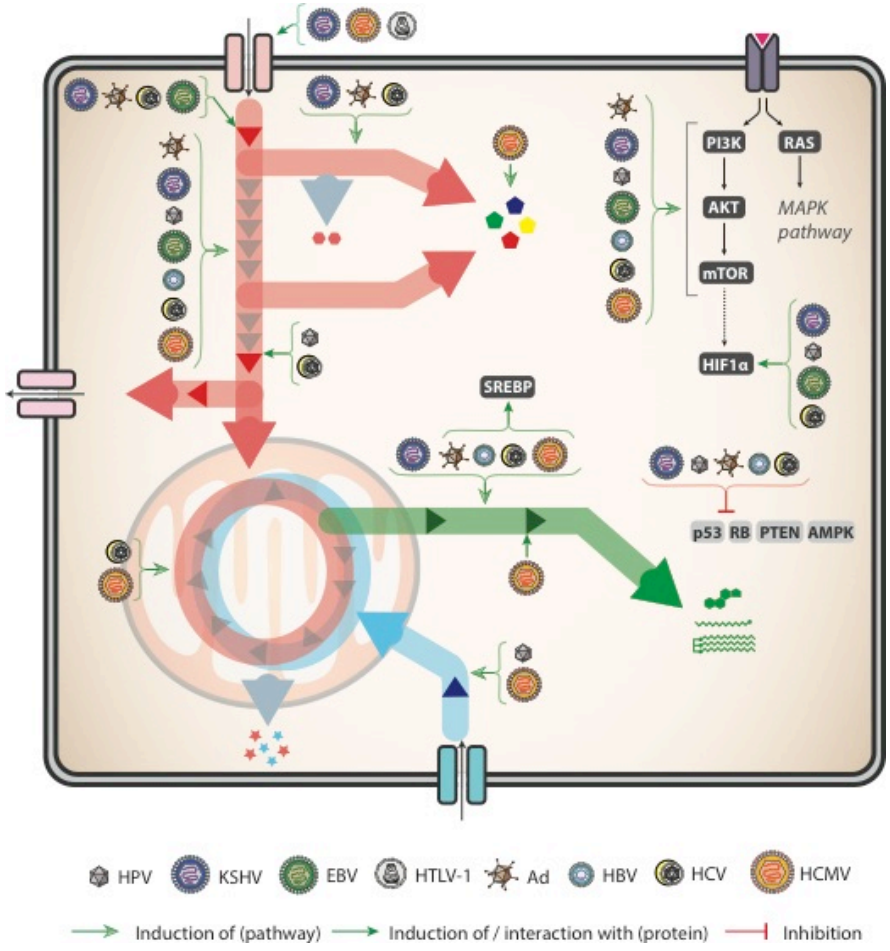
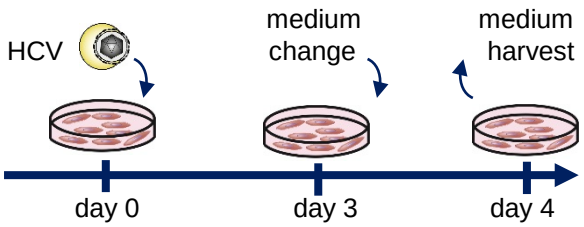
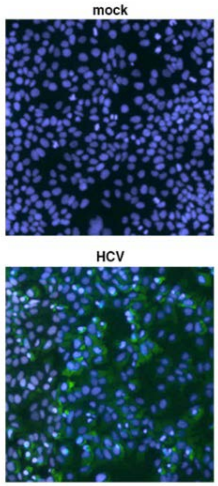
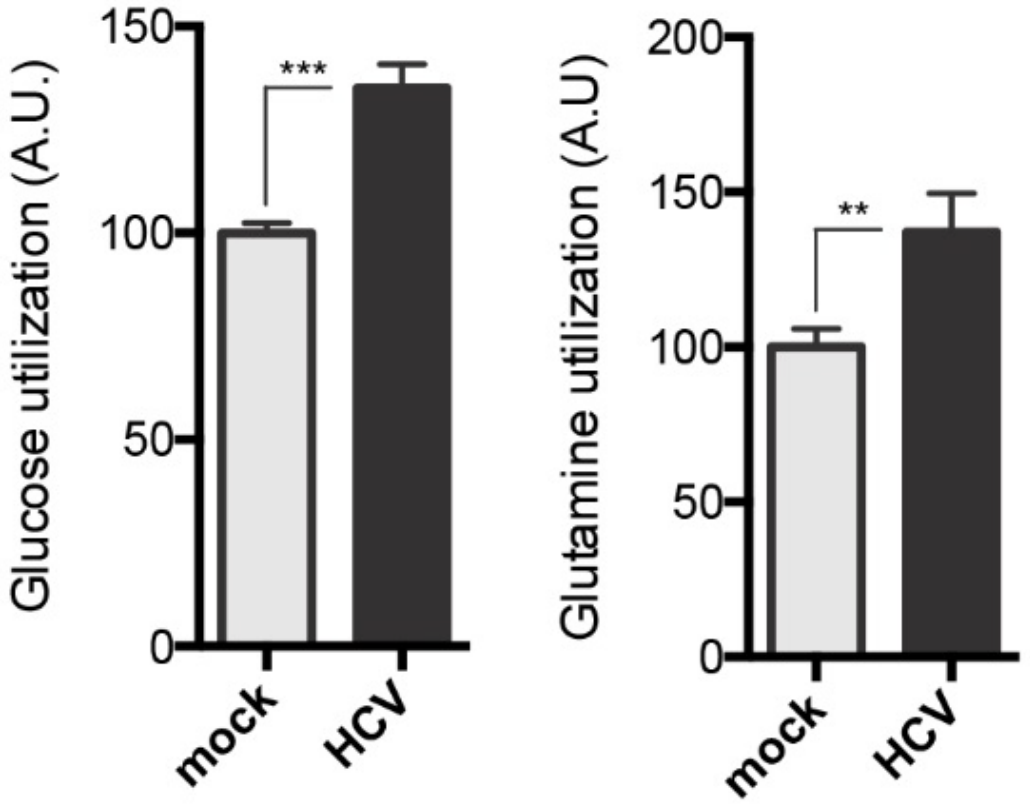




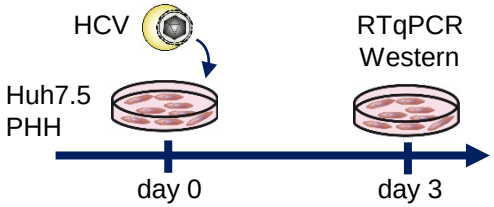
HCV upregulates glucose and glutamine utilization



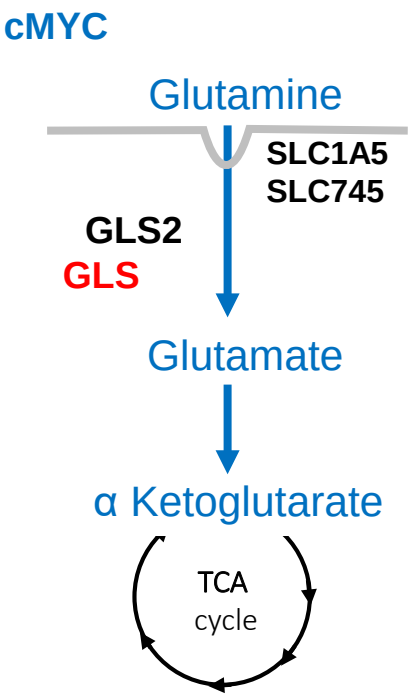




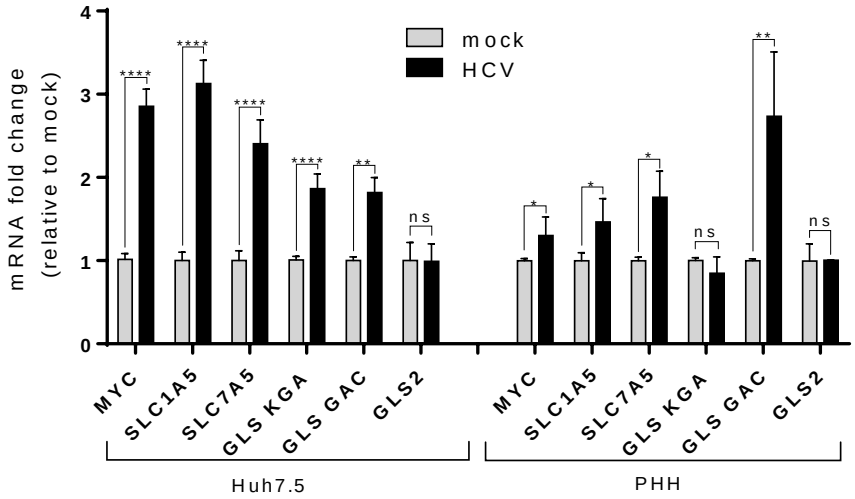
HCV upregulates key factors of glutamine metabolism



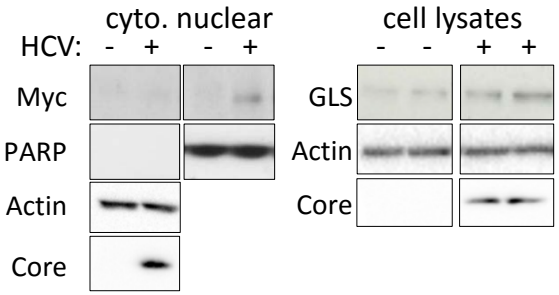
Glutaminolysis



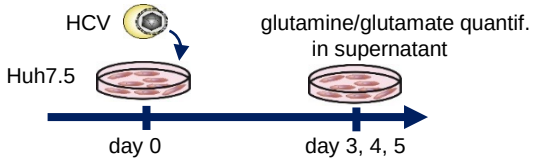
Transcript levels



Protein levels

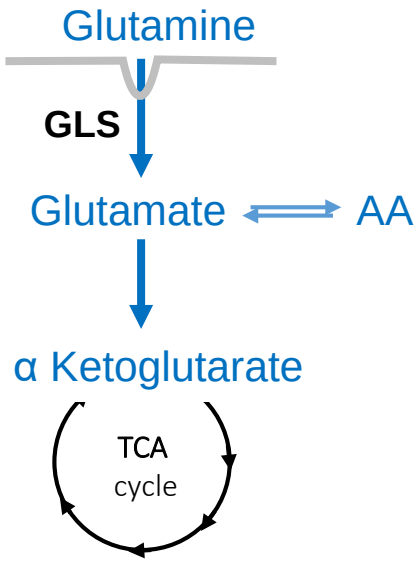


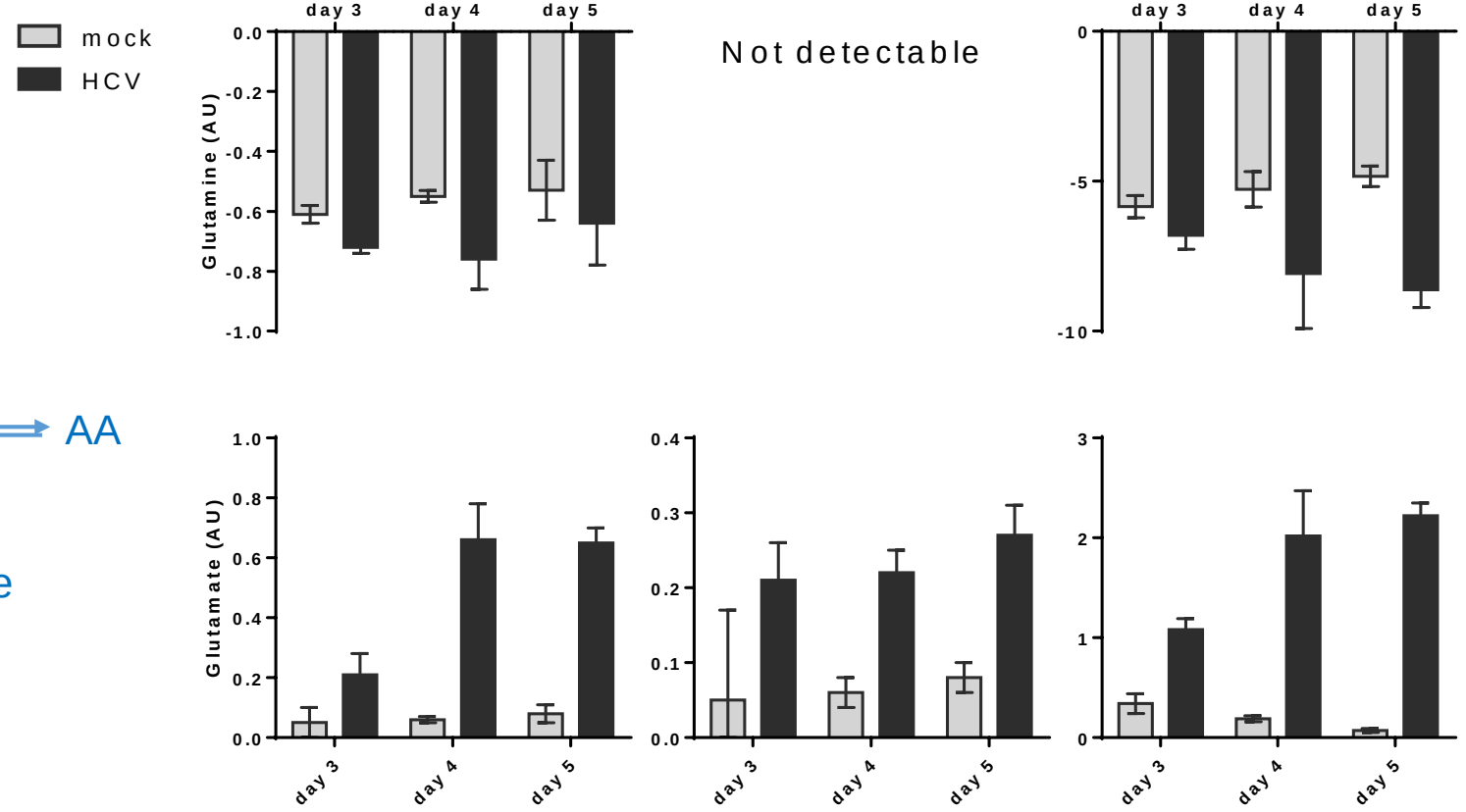
HCV decreases glutamine and induces glutamate levels in supernatant



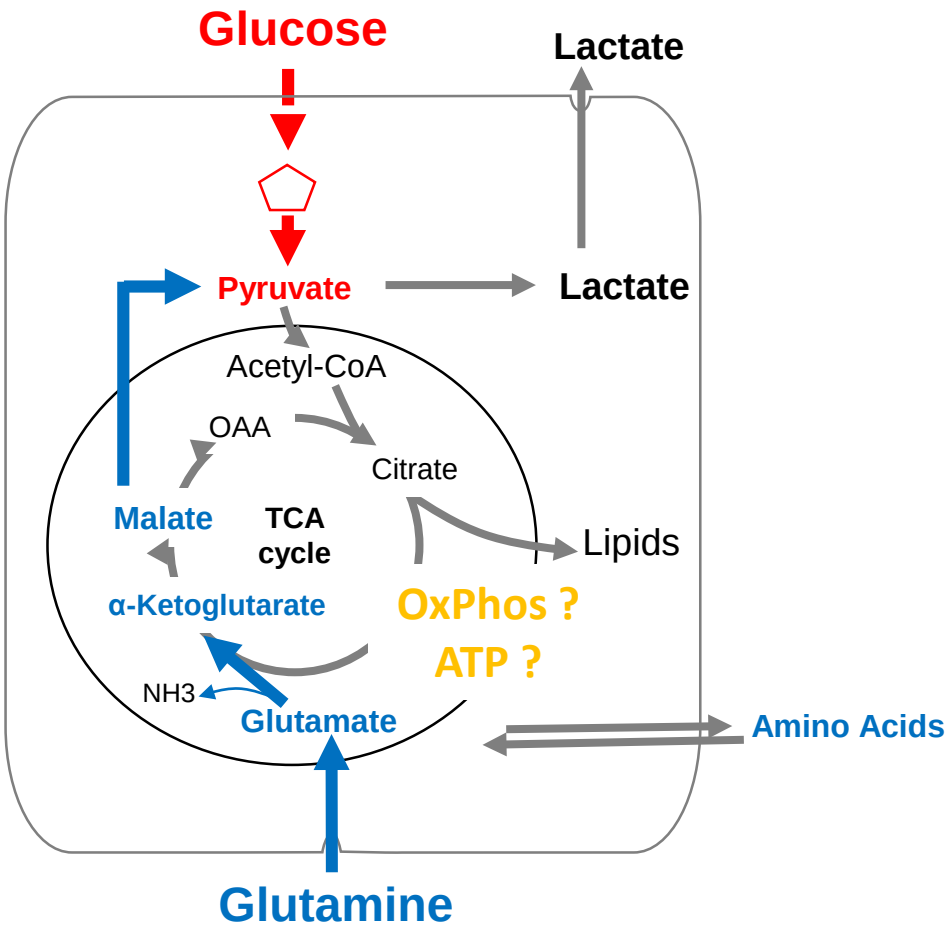
Medium with:

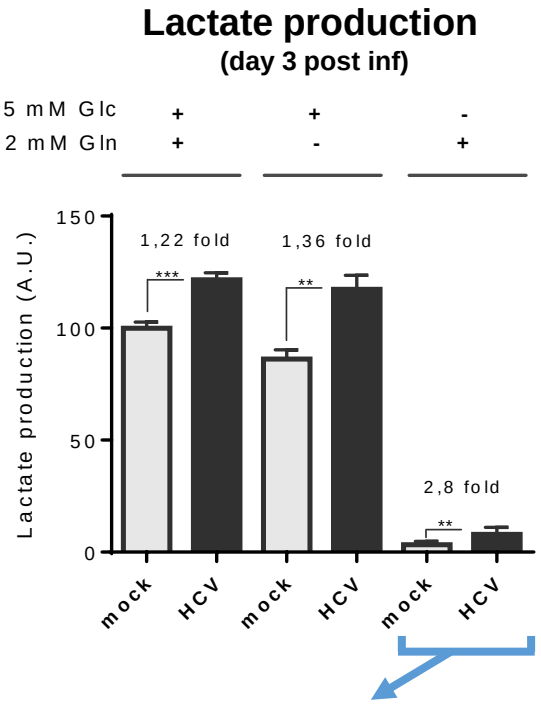
Glucose/Glutamine | Glucose/ - | -/ Glutamine

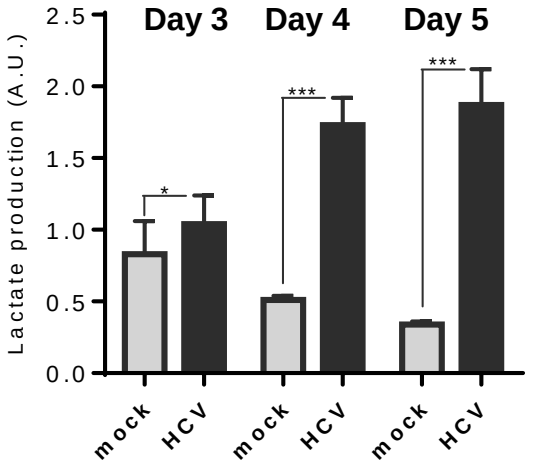




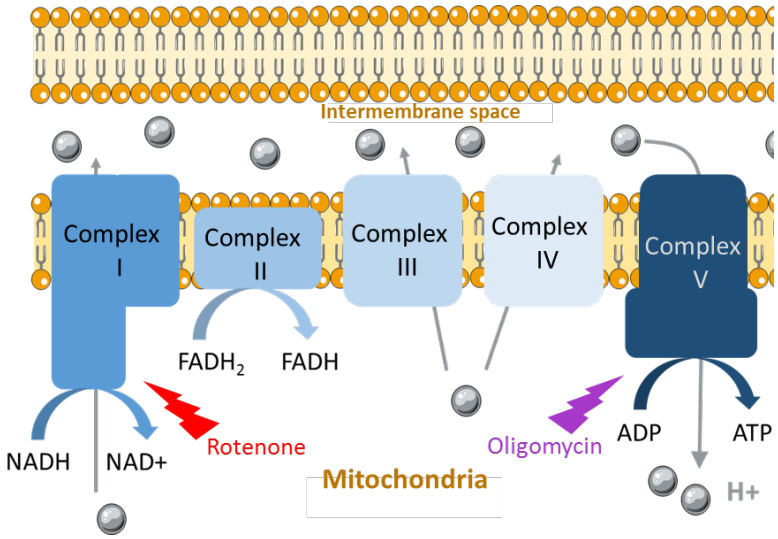
Glycolysis versus glutaminolysis?

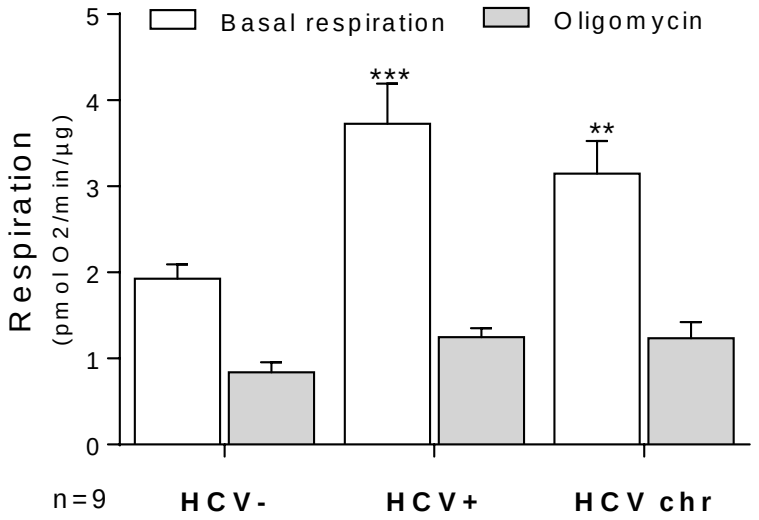


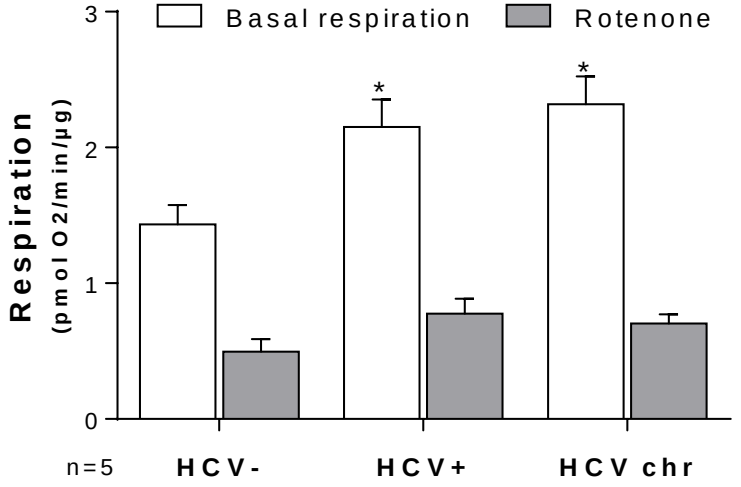




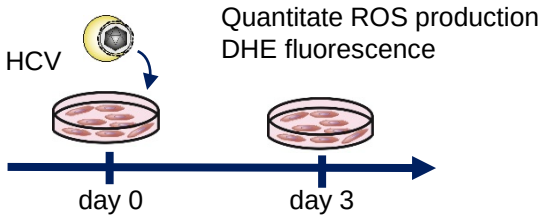
Increased respiratory activity in HCV-infected cells

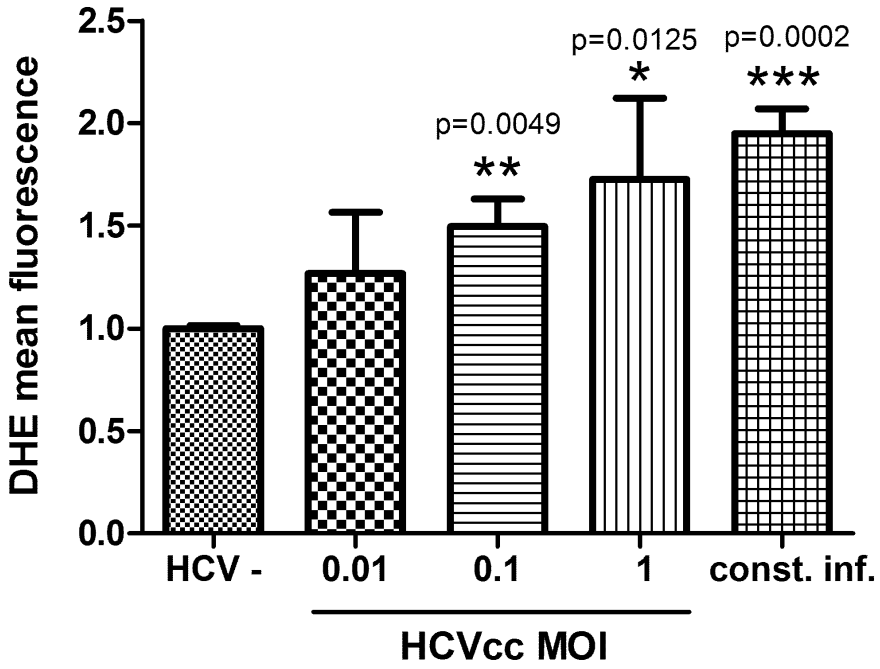






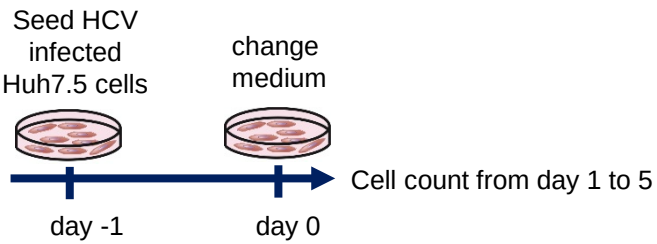
HCV augments superoxide anion production

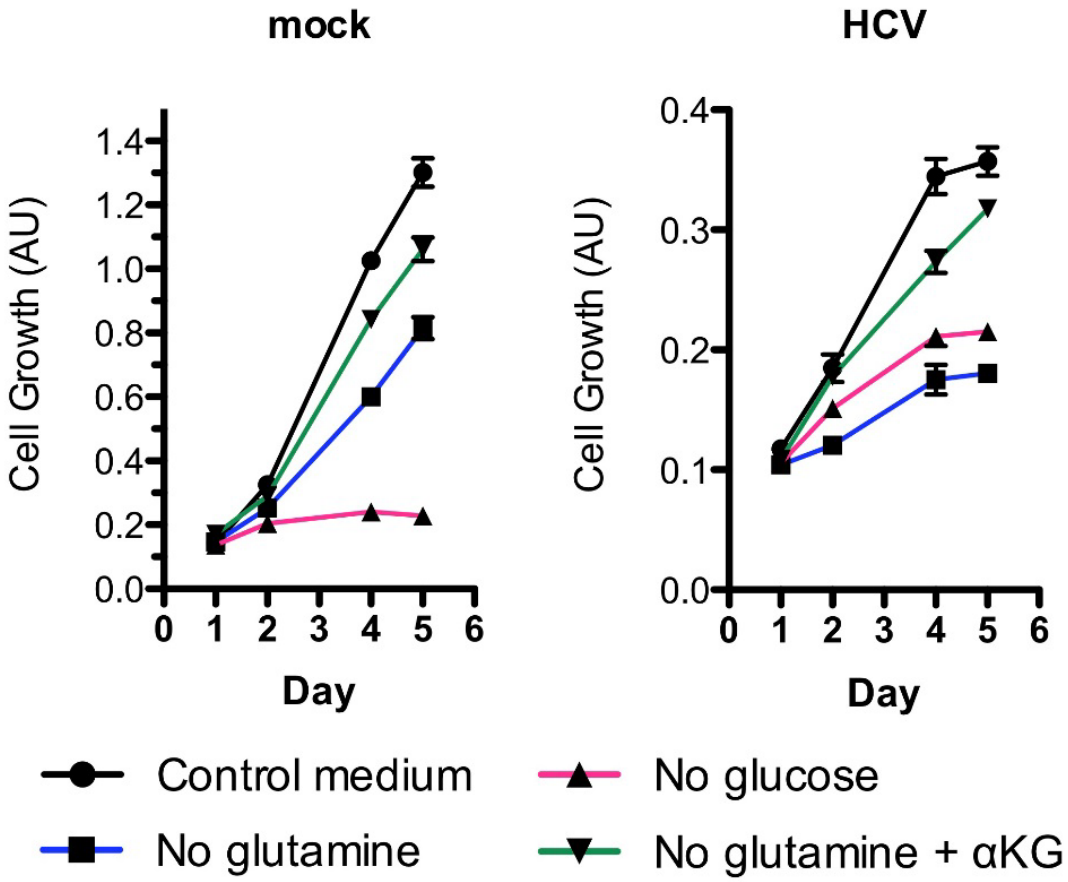




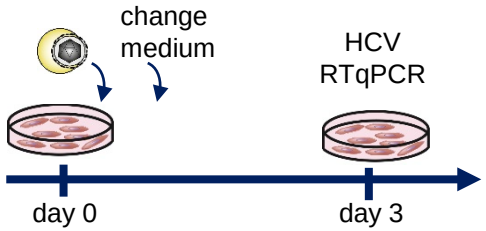
BRAULT et al, GUT 2016

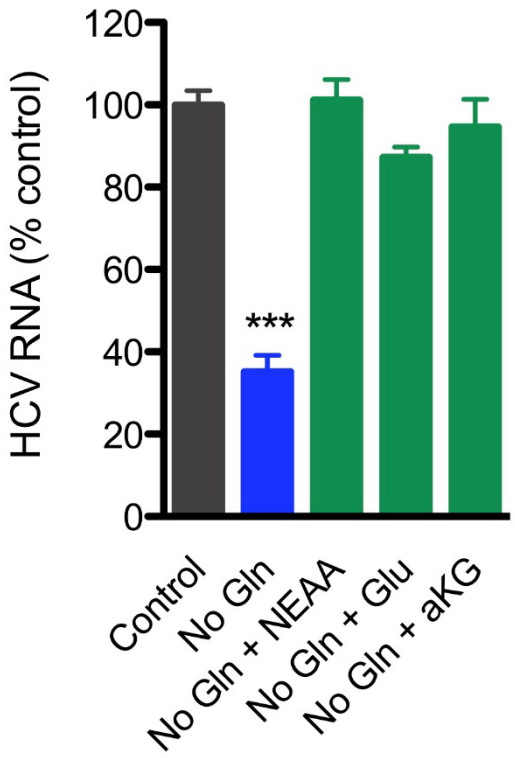
Proliferation of HCV-infected cells depends on glutamine

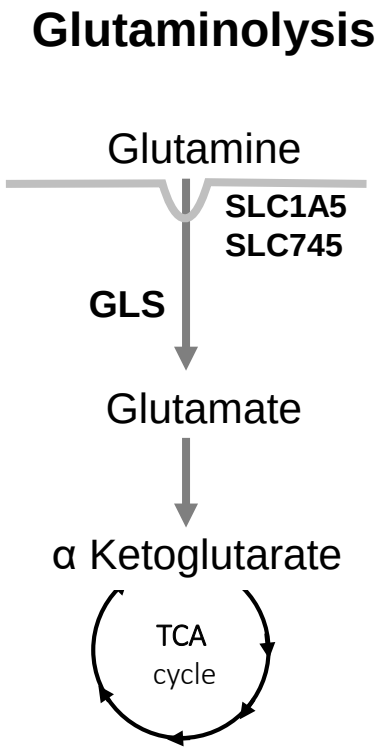




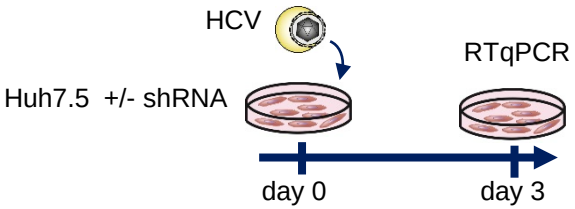
HCV depends on glutaminolysis



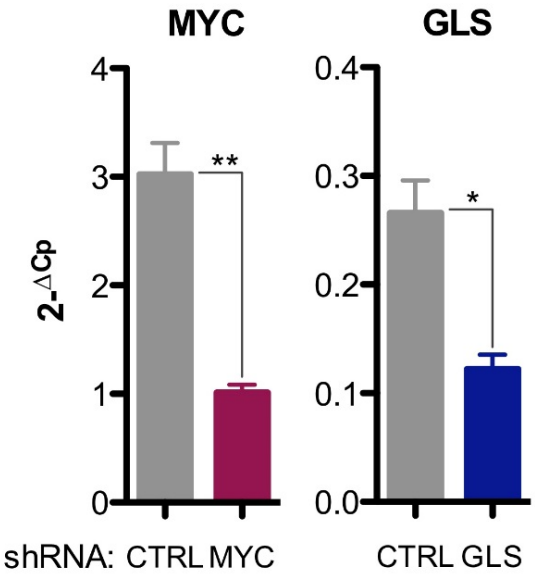




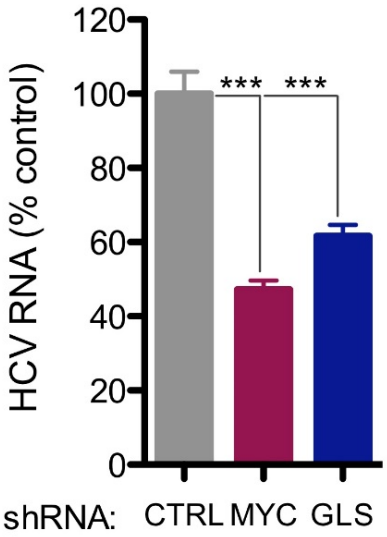
HCV replication is sensitive to MYC and Glutaminase silencing



MYC/GLS silencing efficiency



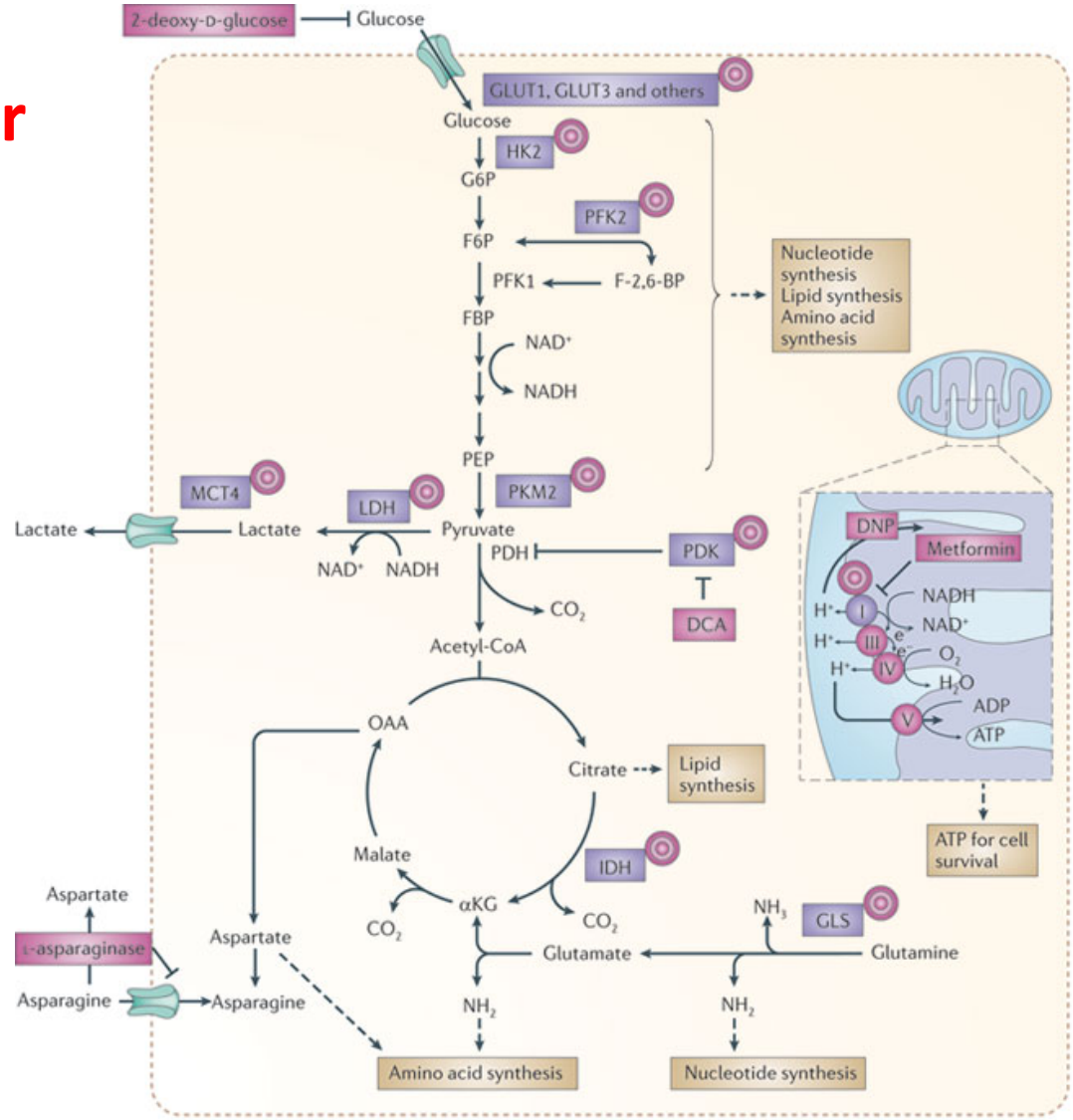
HCV replication



Inhibition of biosynthesis or induction of energy stress

Anti-cancer

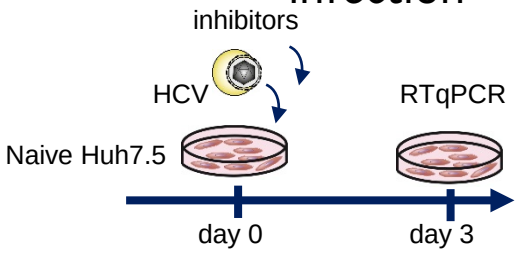
Anti-virus

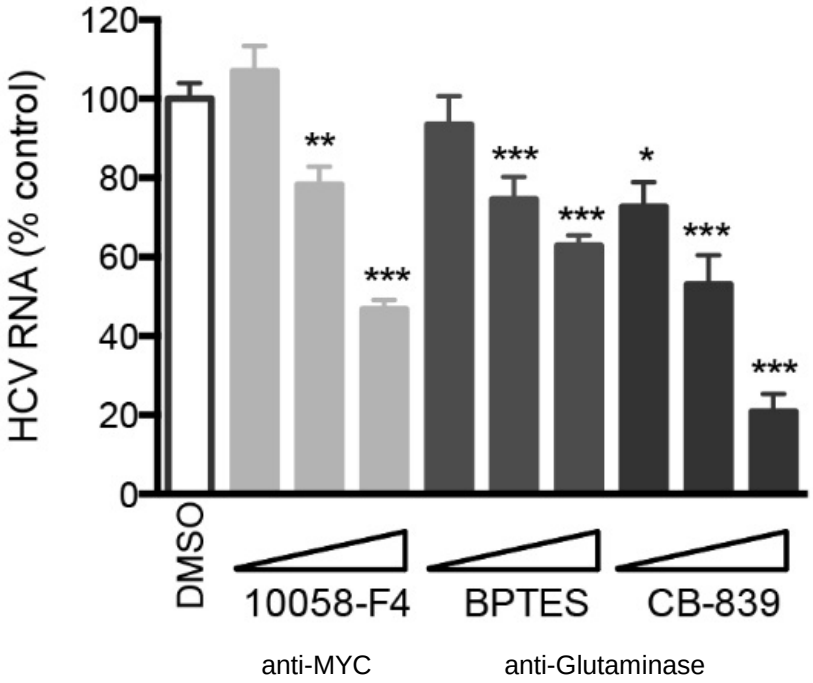


VANDER HEYDEN et al. Nat Rev Drug Disc 2011

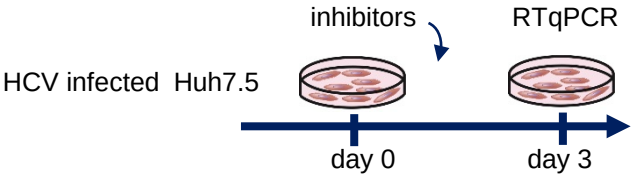
HCV replication is sensitive to MYC and Glutaminase inhibitors

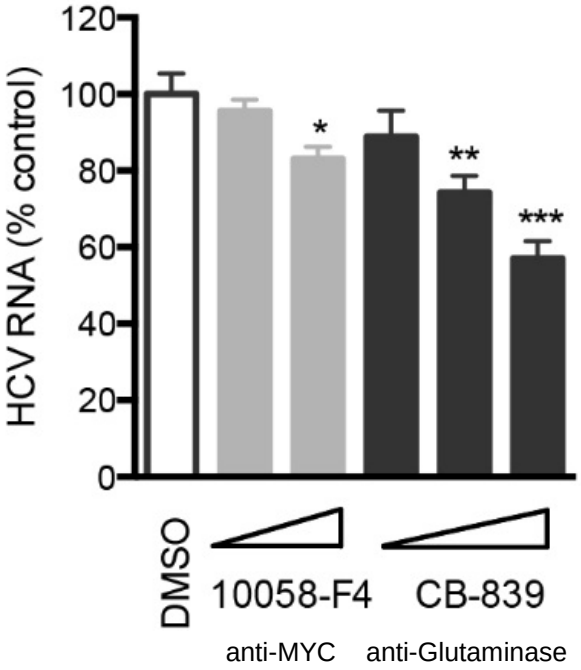
Preventive effect of inhibitors on neo-infection



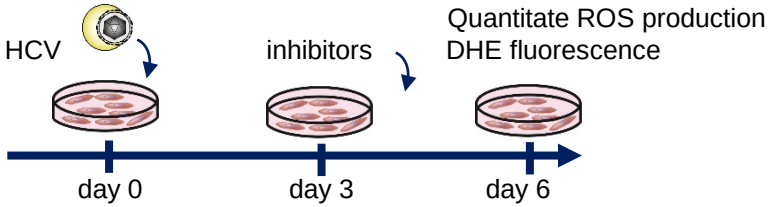


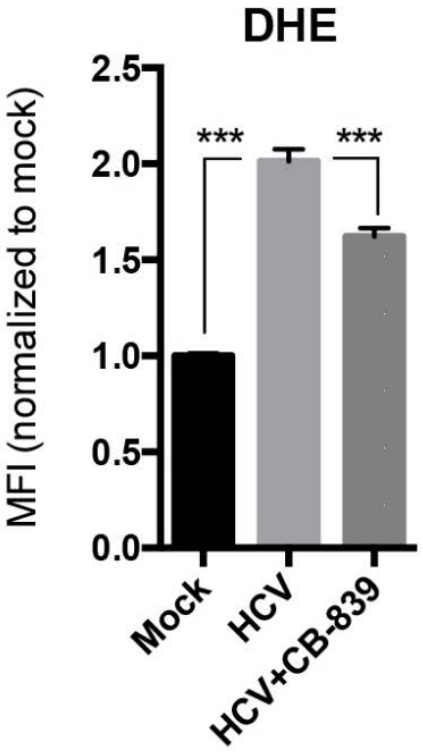
Therapeutic effect of inhibitors on established infection

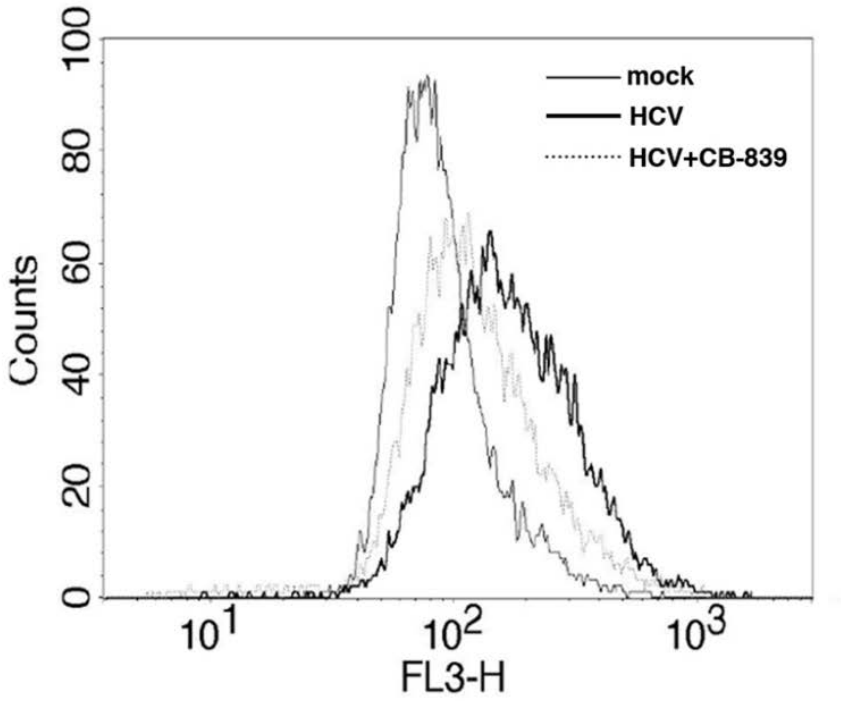




CB-839 blocks HCV-induced superoxide production







Conclusion

Glutaminolysis

- is induced by HCV
- is required for HCV infection
- stimulates cell growth of infected cells in vitro

Importance of glutamine in HCV infection:

→ Redox balance
→ ATP / electron acceptor generation
→ Carbon/nitrogen donor for anabolic processes

What role does glutaminolysis play in fibrosis progression and incidence of hepatocellular carcinoma?

Is induced glutaminolysis reversible, and can we prevent hepatocarcinogenesis by targeting glutaminolysis?

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