O2k brief Infectious
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High-resolution respirometry: Infectious and Liver

Hepatitis C Virus-Linked Mitochondrial Dysfunction Promotes Hypoxia-Inducible Factor 1α-Mediated Glycolytic Adaptation▽†

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Effect of long-term Hepatitis C Virus (HCV) protein expression on the mitochondrial respiration in UHCVcon-57.3 cells

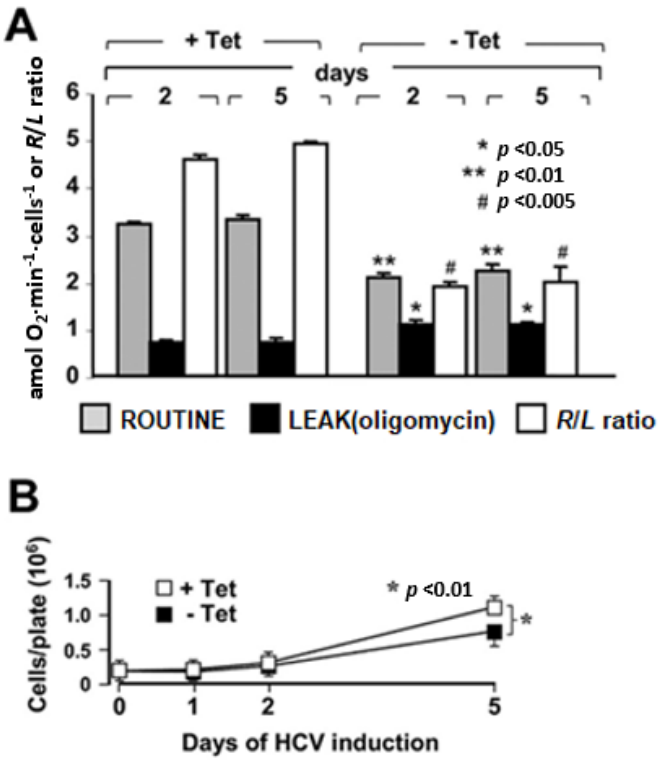

Figure 1. (A) Respiratory activity of living UHCVcon-57.3 cells. Measurements of oxygen consumption were performed by high-resolution respirometry. Repression of HCV protein expression is indicated as +Tet (i.e., medium supplemented with 1 µg/ml tetracycline); derepression of HCV proteins is indicated as -Tet (i.e., medium without tetracycline). The incubation time is also shown. ROUTINE (*R*); LEAK (oligomycin), LEAK (*L*) respiratory activity in the presence of oligomycin. The values represent averages of six independent cell preparations plus standard errors of the mean (SEM); the *p* values reported are versus the non-HCV-induced condition. **(B)** Cell growth analysis. Light microscopy images of noninduced (+Tet) cells and cells induced (-Tet) for 1, 2, and 5 days. Cell numbers are shown. The results are averages of five independent assays ± SEM; the statistical significance versus control cells is shown.

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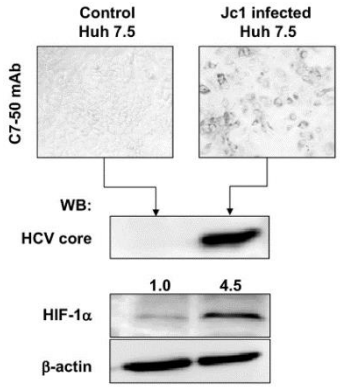
Supported by project NextGen-O2k which has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 859770

Figure 2. Stabilization of HIF-1α in HCV-infected Huh-7.5 cells. Huh-7.5 cells were infected with Jc1 HCV and analyzed 4 days after infection. (Top) Micrographs of cells stained for HCV core protein, as revealed by MAb C7-50 and a horseradish peroxidase-conjugated secondary antibody. (Bottom) Representative (out of three independent preparations) Western blots (WB) of cell lysates for HCV core, HIF-1α, and β-actin. Relative densitometric values for HIF-1α normalized to β-actin are indicated.



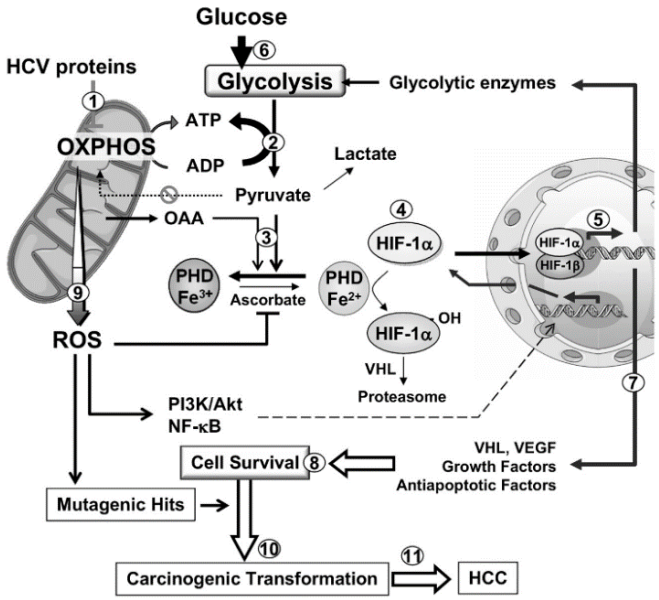


Figure 3. Proposed mechanism for the HCV-linked normoxic stabilization of HIF-1α and its pathogenic implications. The impairment of the mitochondrial electron transfer and phosphorylation systems caused by HCV proteins (1) is suggested to induce a metabolic shift toward glycolysis. This persistent metabolic setting would cause accumulation of pyruvate and Krebs cycle intermediates (2). These are proposed to inhibit the HIF prolyl hydroxylases (PHDs) (3), thereby stabilizing HIF-1α (4). Nuclear translocation of HIF-1α and transactivation of hypoxia-responding genes would upregulate the expression of glycolytic enzymes (5). Therefore, a positive feed-forward mechanism is activated (6). Moreover, as a "side effect," other HIF-dependent angiogenetic and prosurvival factors are upregulated (7 and 8). These events, in combination with HCV protein expression-dependent ROS overproduction (9), may eventually lead to carcinogenic transformation (10 and 11). OAA, oxaloacetate; HCC, hepatocellular carcinoma.

Expression of HCV proteins in a liver cell line affects cell respiration and bioenergetics. This paper proposes that these changes in mitochondrial respiration are involved with PHD inhibition and HIF-1α stabilization, potentially leading to the development of hepatitis C-linked carcinogenic transformation.

Reference: Ripoli M, D'Aprile A, Quarato G, Sarasin-Filipowicz M, Gouttenoire J, Scrima R, Cela O, Boffoli D, Heim MH, Moradpour D, Capitanio N, Piccoli C (2009) Hepatitis C virus-linked mitochondrial dysfunction promotes hypoxia-inducible factor 1α-mediated glycolytic adaptation. J Virol 84:647-60.

Text slightly modified based on the recommendations of the COST Action MitoEAGLE CA15203. Doi:10.26124/mitofit:190001.v6

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