Twitter Thread by Amy Proal, PhD

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Happy 2021! @MBVanElzakker and I are excited to share our new article published in #Immunometabolism: “Pathogens Hijack Host Cell Metabolism: Intracellular Infection as a Driver of the Warburg Effect in Cancer and Other Chronic Inflammatory Conditions”:

2/ In the paper, we detail molecular mechanisms by which #viral, #bacterial, and #parasite intracellular pathogens can induce, or contribute to, a Warburg-like #metabolism in infected host cells in order to meet their own replication and nutritional needs.

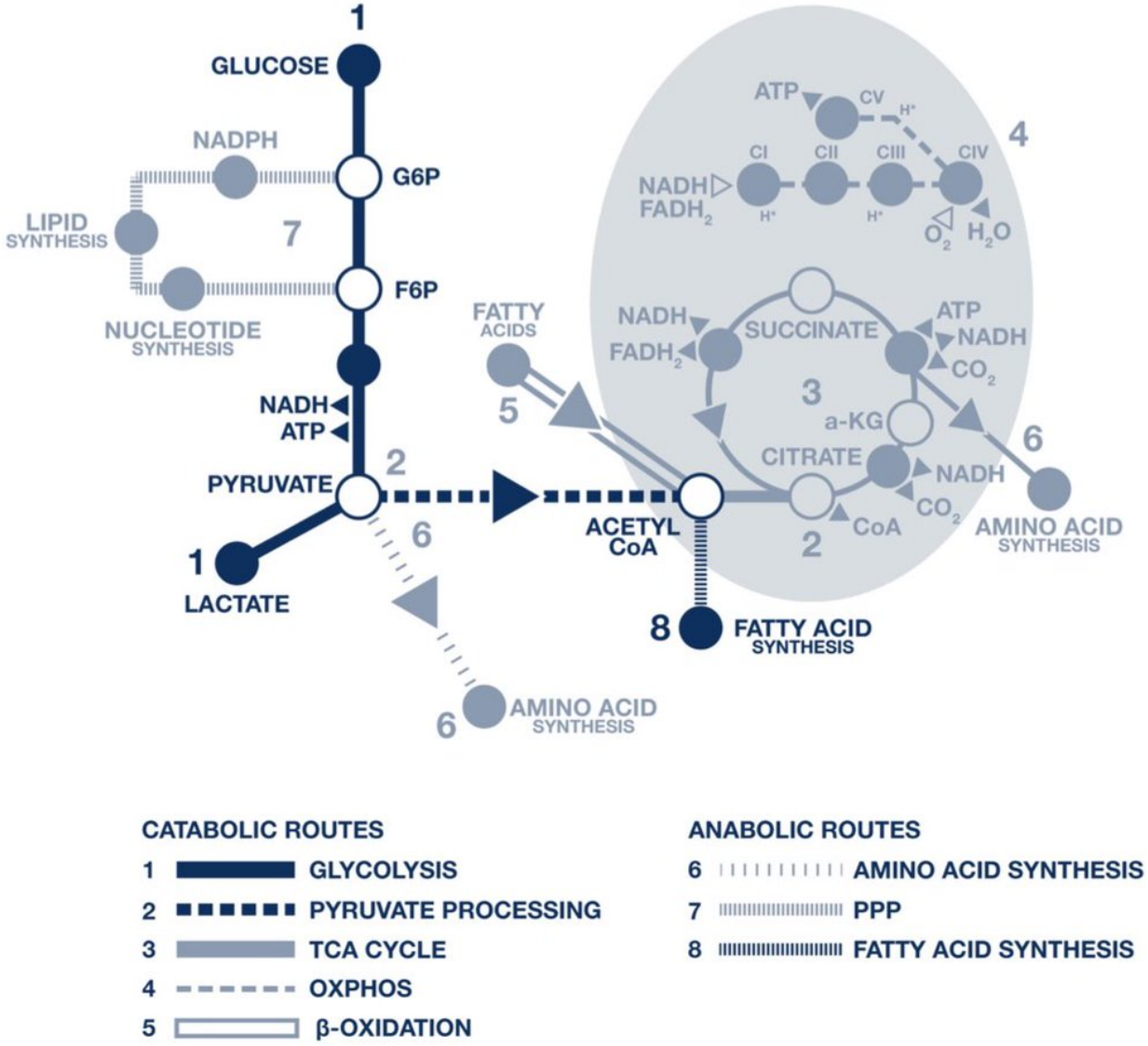

Figure 1. Warburg-like metabolic programs activated upon infection of primary human cells with *Mycobacterium tuberculosis*. Anabolic pathways require an energy input to construct macromolecules such as lipids, nucleic acids, and proteins. Catabolic pathways break down molecules that are oxidized to release energy or for use in anabolic reactions. Reproduced from [2], copyright © 2018 John Wiley and Sons.

3/ We also discuss how host defense towards #infection may impact cellular metabolic changes (including how #mitochondria can participate in the innate immune response towards infection)

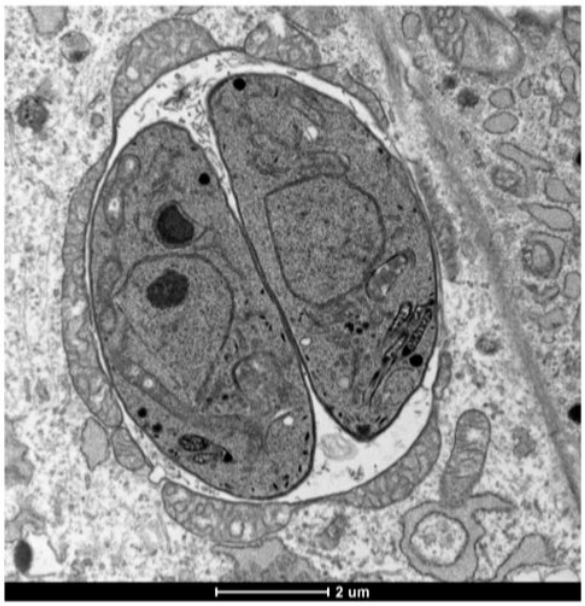

Figure 3. Murine fibroblast mitochondria encircle and are tethered to the vacuole in which *Toxoplasma gondii* replicates. Image courtesy of Dr. Lena Pernas.

4/ We then provide examples of how many of these same intracellular pathogens have been identified in #tumors, atherosclerotic lesions, #granuloma, and other tissues containing cells with a Warburg or altered metabolism.

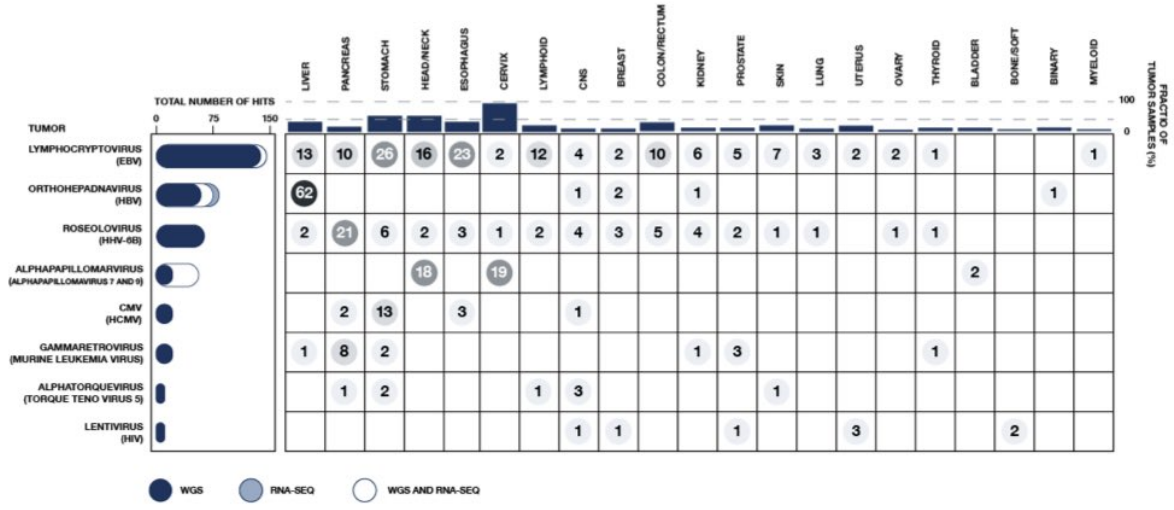

Figure 4. Viruses found in different cancer types with the fraction of virus-positive samples shown at the top. This figure depicts a consensus approach for sequencing-based viral discovery across 389 tumors from 356 patients with cancer. Top of figure depicts fraction of virus-positive tumor samples with viral hits. Grid numbers reflect number of viral hits for each cancer entity. (WGS: Blue, RNA Sequencing: gray). Adapted from [28], an open access article distributed under the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

5/ Last, we examine further trends associated with infection and host cell metabolism, including how #pathogen-driven hijacking of host cell lipid metabolism can support viral, bacterial, and parasite survival and replication.

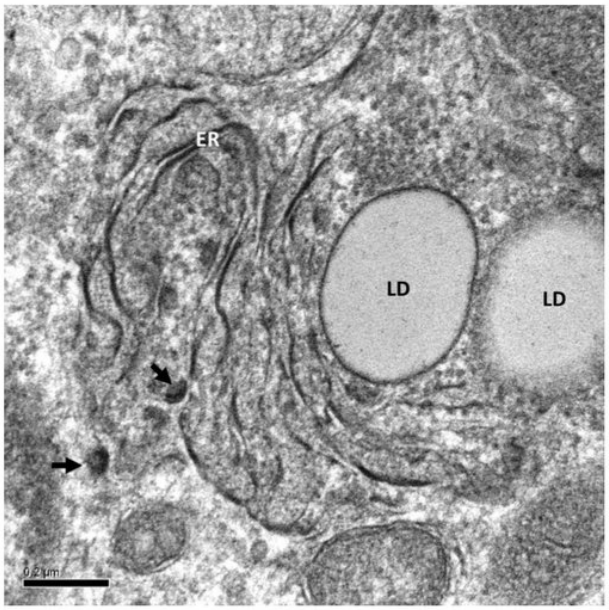

Figure 6. Hepatitis C virus (arrows) bud at endoplasmic reticulum (ER) membranes closely associated with lipid droplets (LD). Image courtesy of Dr. Philippe Roingeard.

6/ Overall we argue that, at least in a subset of patients w/ #cancer, #atherosclerosis, #sarcoidosis + related conditions, metabolic changes and inflammatory cascades central to the disease process are driven by intracellular pathogens

7/ We also discuss how pathogen-driven hijacking of cellular metabolism may contribute to #MECFS. ME/CFS is an extremely debilitating #neuroinflammatory condition that often begins with an infection (w/ #herpesvirus or enterovirus involvement already documented in some cases)

component of amyloid plaques. Interestingly, in separate studies, *P. gingivalis* has been shown capable of promoting oral carcinogenesis, in part by dysregulating host cell fatty acid metabolism [151].

Neurotrophic pathogens have also been tied to the development of Parkinson's disease, myalgic encephalomyelitis (ME/CFS) [152,153], multiple sclerosis [154], schizophrenia, and even epilepsy [155]. For example, Dourmashkin et al. used both transmission electron microscopy and immunohistochemistry to study autopsied brain samples obtained from patients with late-stage Parkinson's disease [156]. They identified virus-like particles and enterovirus antigens in Parkinson's brainstem neurons (Figure 5).

8/ A better understanding + acceptance of the trend could result in novel #diagnostics and treatments for patients w/ such conditions (w/ discussion of how a #ketogenic diet might impede pathogen-hijacking of host metabolism)

9/ So many cool people helped make the paper a reality. Special thanks to @lenapernas @Palmer_IMet_lab @dbkell, Dr. Wonder Drake, and @krisfobes for helping us with feedback and on earlier drafts of the manuscript.