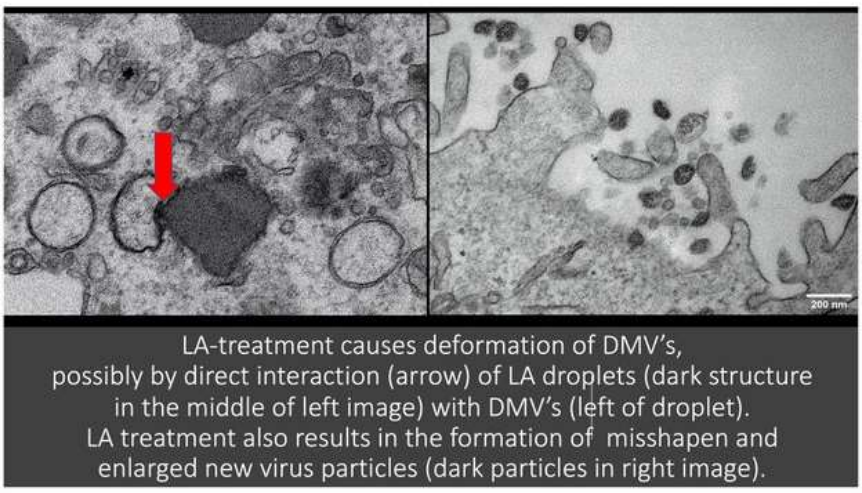
Mechanism of Linoleic Acid protection against SARS-CoV-2 viral replication in human cells

0**Supervisory team:**
Main supervisor: Prof Paul Verkade (University of Bristol)
Second supervisor: Prof Christiane Berger-Schaffitzel (University of Bristol)
Prof Andrew Davidson (University of Bristol)

Collaborators: Prof Imre Berger (University of Bristol)

Host institution: University of Bristol

Project description:



LA-treatment causes deformation of DMV's, possibly by direct interaction (arrow) of LA droplets (dark structure in the middle of left image) with DMV's (left of droplet). LA treatment also results in the formation of misshapen and enlarged new virus particles (dark particles in right image).

The SARS-CoV-2 coronavirus is still having a devastating effect on society where COVID-19 has shut down many aspects of normal life and new variants of the virus appear to influence the efficacy of vaccines dramatically. During infection, SARS-CoV-2 rearranges host cell membranes, forming large amounts of double-membraned vesicular structures (DMVs) in the cytosol, termed replication complexes (RC). Inside, the viral genome is replicated before being packaged into new viral particles.

We have found that a small fatty acid, Linoleic Acid (LA), is able to bind with high affinity to the Spike protein of SARS-CoV-2 (Toelzer et al., 2020). Upon binding, LA traps the spike protein in a non-infectious, "closed" conformation and inhibits interactions with the receptor of the human host cell, thus providing an avenue for antiviral therapy. Besides this direct effect on binding, we (collaboration between the Verkade, Berger-Schaffitzel, and Davidson groups) have recently found that viruses that do manage to infect LA-treated cells produce DMVs and new viruses that are misshapen as shown by electron microscopy (see Figure). Also, the number of viruses produced per cell appears to be lower.

LA treatment generates LA droplets in the cell, and when infected with the SARS-CoV-2 virus there appeared to be direct connections between these droplets and the DMV's that are packaging new virus particles. Therefore, we hypothesise that LA may inhibit the membrane remodelling induced by the virus, suppressing the formation of RCs. LA thus may interfere with an essential step in viral replication which is conserved across coronaviruses and SARS-CoV-2 variant-independent.

This project aims to elucidate the mechanism of LA-treatment on SARS-CoV-2 infection and replication. As a successful candidate you will work in a highly interdisciplinary environment between the groups of Professor Andrew Davidson, a specialist in coronavirus biology, Professor Christiane Berger-Schaffitzel, a cryo-EM expert and Professor Paul Verkade, cell biologist and imaging expert.

Focussed around state-of-the-art imaging approaches such as cryogenic electron microscopy (EM), 3D electron tomography, and correlative light electron microscopy (CLEM, Hodgson et al., 2017) and using uniquely available fluorescent coronavirus and expertise in virus biology, you will aim to elucidate the molecular mechanism of action of LA and collaborate on this very exciting area of research.

References: - Toelzer et al., 2020, Science, doi: 10.1126/science.abd3255 - Hodgson et al., Methods in Molecular Biology, Volume 1836: Influenza virus, 237-260.