Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Statins may be a key therapeutic for Covid-19

The article by Neal M. Alto PhD, et al in the April 13, 2020 issue of Nature Microbiology describes how macrophages protect mucosal epithelial cells from listeria monocytogenes infection by a mechanism that makes epithelial cell surface cholesterol inaccessible [1].

That observation leads one to wonder if a similar effect protects against SARS-CoV-2 infection.

Epithelial cell plasma membrane lipid raft physiology is central to the infectivity of SARS-CoV-2 since the ACE2 receptor for SARS-CoV-2 is part of the lipid raft.

A lipid raft is a plasma membrane domain that has a sphingolipid hydrophobic component, cholesterol, glycosyl-phosphatidyl inositol (GPI) – anchored proteins, other glycolipids, and a specific set of associated proteins, often cell receptors and transduction proteins.

SARS-CoV-2 enters a cell by binding its viral spike protein to the lipid raft ACE2 receptor. But to achieve cell entry, the spike protein also needs to bind its N terminal domain to the sialic acids bound to gangliosides sitting on the lipid raft of which ACE2 is a protein component [2,3].

Hydroxychlorquine and chloroquine have been shown to decrease binding of SARS-CoV-2 to the sialic acids bound to the gangliosides of the lipid raft [3].

Several studies have shown that depleting the plasma membrane lipid raft of the cholesterol component will prevent coronavirus cell entry despite normal virus binding. This has been shown for SARS-CoV, canine coronavirus, murine coronavirus, porcine rotavirus, and other viruses that enter the cell using the lipid raft gateway [4,5,6].

The in vitro studies of lipid raft cholesterol depletion have been done using methyl-beta cyclodextrin (MBCD) to deplete lipid raft cholesterol. In vivo, a candidate drug class that depletes cellular and plasma membrane cholesterol is the HMG CoA reductase inhibiter class known as the statins.

I submit that the statins might cause enough lipid raft cholesterol depletion to decrease SARS-CoV-2 viral entry and infectivity.

An alternative cholesterol lowering drug class, the PCSK9 inhibitors, are known to work by increasing LDL particle uptake by increasing LDL receptor survival. Increased LDL particle uptake with presumably increased lipid raft cholesterol, is the same strategy that dengue fever virus uses to gain entry into huh-7 cells when it binds to lipid rafts [7]. Therefore, PCSK9 inhibitors would be virus infectivity enhancers.

It is interesting that the SARS-CoV-2 fatality rate correlates with cholesterol levels. It has a low fatality rate in children, who naturally have lower cholesterol levels. It has higher fatality in men, diabetics, the obese, the elderly, and the hypertensive, all of whom tend to have higher cholesterol levels. The lower SARS-CoV-2 fatality rate in Asia may be explained in part by lower obesity rates resulting in lower lipid raft cholesterol levels. A higher fatality rate in Europe and Brazil, where the obesity rate is near equivalent to the USA, could be explained by higher lipid raft cholesterol levels.

The Nature online article of 4/30/20 “A SARS-CoV-2 protein interaction map reveals targets for drug repurposing” discussed 69 compounds, of which 29 were FDA approved drugs, that had SARS-CoV-2 human cell protein-protein interactions. Lovastatin was one of the drugs tested in kidney cell culture and it was successful in decreasing percent infection from 100% to about 30% at 10^{-5} M drug concentration [8].

Many of the drug targets in the article have a final common pathway through Sigma receptors. Overexpression of Sigma 1 receptors increases lipid raft cholesterol content and alters glycosphingolipid components in lipid rafts suggesting that up-regulation of Sigma 1 receptors potentiate lipid raft action [9].

Conflict of interests

I have no conflict of interests to report.

References

[1] Vulnerable Cells armor themselves against infection by depleting surface cholesterol. Nature Microbiol; 2020. DOI: 10.1038/s41564-020-0701-5, Neal M.Alto et al. https://nature.com/articles/s41564-020-0701-5 https://www.utsouthwestern.edu/newsroom/articles/year-2020/vulnerable-cells-armor-themselves-against-infection-by-depleting-surface-cholesterol.html.

[2] Lipid Rafts are involved in SARS-CoV entry into Vero E6 cells, Biochem Biophys Res Commun 369(2):2008:344-349. Yanning Lu et al.

[3] Structural and molecular modelling studies reveal a new mechanism of action of chloroquine and hydroxychloroquine against SARS CoV-2 infection. Int J Antimicrob Agents. Online 4/3/20 Sciencedirect.com https://doi.org/10.1016/j.ijantimicag.2020.105960.

[4] Earnest JT, et al. CoV receptors and proteases are transmembrane anchored in lipid raft like microdomains. J Virol 2015;89:6093–104.

[5] Requirement for CEACAMS and cholesterol during murine coronavirus cell entry. J Virol (2004). Edward Thorp, Thomas Gallagher.

[6] Role of the lipid rafts in the life cycle of canine coronavirus. J Gener Virol Annamaria Pratelli et al February 2015.

[7] The increase in cholesterol levels in early stages after dengue virus infection correlates with an augment in LDL particle uptake and HMG CoA Reductase Activity. Virology 442(2):2013;132–147. Ruben Soto-Acosta and Rosa Maria del Angel. https://doi.org/10.1016/J.virol.2013.04.003.

[8] A Sars-CoV-2 protein interaction map reveals targets for drug repurposing. Published online 4/30/2020. David E Gordon et al https://doi.org/10.1038/s41586-020-2286-9.

[9] Sigma receptors: biology in normal and diseased states. Colin G.Rousseaux and Stephanie F. Greene. J Receptor Signal Transd Res 36(4):2016;327–328.

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