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On COVID-19 and Membrane Lipids and Public Health (英文原文)

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Abstract: Coronavirus has a lipid membrane. Whist replication requires hijacking the RNA tools of the host to synthesize virion protein, that then has to be wrapped in a lipid membrane to enable the budding off which extends the infection. Recent studies implicate certain essential fatty acids with replication suppression properties. The lipid membrane is commonly thought of as a fatty barrier to water solubles. It is however highly ordered and compositionally specific to cellular and sub cellular functions. There will likely also be an optimum specificity for the viral coat. Whist DNA, RNA and protein compositions are not affected by diet, the lipid membrane is. Moreover, the greater sensitivity of males over females to inadequacy of these essential fatty acids and membrane integrity has been known since the 1960 s. With evidence that arachidonic and docosahexaenoic acids exhibiting anti-viral, immune, anti-inflammatory, blood pressure control and resolvin activity, their status needs to be urgently examined in relation to the prevention and therapy for Covid-19. It would also be advisable to re-assess food policy. The lipid requirements for the membrane rich systems as in the brain, nervous, vascular and immune systems have not been considered. There is little doubt these were significant in shaping the human genome over several million years. Departure from such conditions would be predicted to put populations at risk to disorder and infection, with males being more at risk than females.

Key words: coronavirus; Covid-19; arachidonic; docosahexaenoic; membrane lipid; male-female risk public health

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ABBREVIATIONS

BAME: Black, Asian and Minority Ethnic

SARS-CoV: Severe Acute Respiratory Syndrome Coronavirus

MERS-CoV: Middle East Respiratory Syndrome Coronavirus

S: Spike

ACE2: Angiotensin-Converting Enzyme 2

LA: Linoleic Acid

ArA: Arachidonic Acids

DHA: Docosahexaenoic Acid

EPA: Eicosapentaenoic Acid

PE: Phosphatidyl Ethanolamine

PD: Protecin

FADS: Fatty Acid Desaturase

OPH: Optimum Physics Hypothesis

NCD: Non-Communicable Disease

1. CORONAVIRUS, AND ESSENTIAL FATTY ACIDS

This paper has been written to draw attention to the significance of essential fatty acids to the cell membrane and their possible involvement in the access of corona virus to the interior of the cell and the requirement of a lipid membrane in the budding off of the virus during replication. Because essential fatty acids are involved in this process, then the background diet which is a determinant of membrane integrity will become important in sensitivity to infection, its consequences and could be relevant to the greater susceptibility of Black, Asian and Minority Ethnic (BAME), males compared to females and to therapy.

A recent study reported in Science on the structure of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) spike (S) glycoprotein described how receptor domains bind linoleic acid (LA) in three composite binding pockets. A similar pocket was also described in the highly pathogenic severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV).

The authors reported invitro studies which showed that the LA binding resulted in a reduced angiotensin-converting enzyme 2 (ACE2) interaction. “In human cells, LA supplementation synergizes with the COVID-19 drug remdesivir, suppressing SARS-CoV-2 replication. Our structure directly links LA and S, setting the stage for intervention strategies that target LA binding by SARS-CoV-2[1]”.

Yan B et al. [2]also reported early 2019 on the behaviour of fatty acids to human coronavirus 229E (HCoV-229E) as a “model coronavirus to comprehensively characterize the host cell response upon coronavirus infection.” They reported the inhibitory effect of LA and Arachidonic Acids (ArA) on virus replication, and showed the inhibitory effect was also “conserved for the highly pathogenic MERS-CoV.” This report was prior to the outbreak of Covid-19 but could be relevant as they were dealing with the same family. They comment as above, “data further suggested that lipid metabolism regulation would be a common and druggable target for coronavirus infections”.

ArA is a metabolic product of LA but is preferentially incorporated into cell membranes, especially those of the endothelium[3], immune cells[4-5] and the brain[6-7]. Metabolism would include the Fatty Acid Desaturase (FADS) enzymes involved in the conversion of LA to ArA which has been suggested as a likely variable in risk[8].

2. THE SIGNIFICANCE OF THE VIRAL AND CELL, LIPID MEMBRANE

The plasma membrane of the cell is a lipid bilayer and it represents the cell’s interface with the outside environment. The lipid bi-layer, also is home to about a third of the known cellular proteins. These are the transporters, ion channels, anti-oxidants, receptors, cell recognition, signalling systems including ligands for nuclear receptors[9]. Its composition is tightly conserved in the context of cell-specific type. Coronaviral infectivity depends first on interactions between components of the host cell with the fusion of the virus envelope and the cell’s plasma membrane[10].

Covid-19 is an enveloped viruses consisting of a protein encased in lipid membrane. It has to cross the host cell plasma membrane. Yan et al comment “coronaviruses precisely modulate and rearrange the host lipid profile to reach an intricate homeostasis optimized for its replication”. Viral replication is achieved by hijacking the host’s tools, wrapping the viral protein in a lipid membrane and then budding off to replicate elsewhere[11].

The host lipid profile therefore is intimately involved in envelope bound viruses of which Covid-19 is one[12]. “Any exogenous manipulation that disrupts the equilibrium may interfere with the optimal replication of the viruses”. The synthesis of lipid for the viral coat is essential to its replication as shown in studies on dengue virus replication[13]. It seems arachidonic and linoleic acid does the trick①, although

① Arachidonic acid in the cell membrane is accompanied by the eicosatrienoic precursor and tetra-enoic elongation product, adrenic acid. The former relevant to blood flow and the latter to corticoid metabolism in adrenals.

probably in partnership with other fatty acids[14].

3. DOCOSAHEXAENOIC ACID AND PROTECTION

It is likely that docosahexaenoic acid (DHA) and possibly eicosapentaenoic acid (EPA) also have a role to play via their anti-inflammatory and cell protection properties[15-16]. Recently discovered is a novel protectin D1, a derivative of DHA which has a viral protective property[17]. Their study showed that PD1 inhibited the direct interaction between viral RNAs and the mRNA exporter NXF1 hence suppressing viral replication. Similar evidence on efficacy of DHA has been reported for the influenza virus[18] with a review in progress[19]. DHA derived lipid mediator protectins (i.e., PDX, PD1), have been shown to suppress influenza virus replication through a mechanism that blocks export of viral mRNA[9].

Host lipids are indispensable for the virus envelopes and so the structural integrity and functionality of virions. There is a common view that lipids are random collections of molecules. They clearly are not. Even the nuclear lipids have been shown to be highly ordered[20]. This ordering will be purposeful to meet the needs of the local functions: what the late Myer Bloom described as the Optimal Physics Hypothesis (OPH)[21].

4. THE INNER CELL MEMBRANE IS RICH IN ARA AND DHA

The phosphatidyl ethanolamine (PE) is the most prominent inner cell membrane lipid and is rich in ArA. It is interesting that at a time of a high immune system challenge, namely birth, the immune cells ethanolamine phosphoglycerides contain some 47% ArA, with functional immune system relevance[5].

The polyenoic fatty acids are in the sn2 of the phosphoglycerides. There is only one other position available the sn1, which is occupied by saturated fatty acids. Hence 47% is close to the limit of 50%. Is Nature telling us something about ArA and immune function[4]?

In the brain's signalling membranes by contrast, the PE is rich in DHA. The balance of the fatty acids is highly conserved and has been found to be essentially the same across many species[22]. Compositional conservation is spread across the different organs evidently with a specificity for separate functions, as for example the vascular endothelium, mitochondria and nuclear envelope consistent with the concept of OPH. The implication is that a balance exists between ArA and DHA which provides for optimal membrane function and integrity. Oleic acid has been found to correlate with increasing natural killer cells in maternal blood and is a marker for these fatty acids in the membrane[5].

These highly ordered lipids will be critical for membrane fusion during virus infection into host cells and replication. ArA and DHA will also be principle anchors for lipid ordering. ArA and its precursor, linoleic acid are diet dependent as is DHA which is mainly available from marine sources. A balance of the land and aquatic based resources for these two fatty acids is likely to have been an accompaniment to the shaping of the human genome in prehistory[23]. Moreover, the greater proportion of male to female deaths is of interest here as males are well known to be far more sensitive to essential fatty acid inadequacy even before birth[24].

5. POTENTIAL RELEVANCE TO PREVENTION, TREATMENT AND THE FOOD SYSTEM

Whilst the significance of the lipids in health and disease has been described by three joint consultations of FAO and WHO[25-27], on the negative side, there is yet to be any proper guidance from government resources in any country on requirements for health, immune, vascular and neural integrity or their protection in the food web, e.g.[28]. On the positive side their role in the current pandemic of Covid-19 has potential and needs urgently to be assessed[29]. Whilst prevalence data for this infection is affected by many behavioural factors, it is none the less interesting that Japan has the lowest rate of mortality/million infected, amongst the industrialised countries. Traditionally, it also has the lowest mortality from cardio-vascular disease, common cancers and major depression and a link has been suggested between the metabolic syndrome and the severity of the infection[30]. This contrast is frequently attributed to the high fish and sea food intake: that is to a food system which is rich in DHA, trace elements, vitamins A and D.

"Therefore, the enormous structural and functional diversities of lipids highlight their great potential as attractive targets for host-virus interactions at various life cycle stages[22]." They are therefore targets for nutrition in prevention and treatment as well as for pharmacological approaches to prevention and therapy. The brain, vascular and immune systems have in common a high requirement for arachidonic and DHA for the structure, function and integrity of

their cell membranes. Yet no government includes these principles in food policies. The evidence stresses the need to address the food system and its relevance to immune, vascular and mental health, especially during early development[23]. Perhaps the present pandemic is a wakeup call.

Whist DNA, RNA and protein compositions are not affected by diet, the lipid membrane is. The evidence from hospital admission rate for Covid-19 being "synonymous with an elevated risk of non-communicable disease"[31] mirrors the disproportionate mortality from coronavirus on BAME highlighting the longstanding inequalities of health. The Guardian, a UK newspaper (May 27, 2020) quoted the mayor of Bristol, Martin Reeves, arguing that the crisis must be a watershed moment to fix such inequalities.

Bear in mind, the systems with a high dependency on membrane lipids for their structures andfunction are the brain, nervous, vascular, immune and reproductive systems[32]. Mental ill health is now the no 1 burden if ill health, The inequalities for low birthweight, the Non-Communicable Diseases (NCDs) and mental ill-health with the BAME at highest risk, in the UK and USA at any rate, have been known for too long [33-34]. A nationwide, cross speciality surveillance study of acute neurological and psychiatric complications of Covid-19 led the authors to conclude that "altered mental status was the second most common presentation, comprising encephalopathy or encephalitis and primary psychiatric diagnoses, often occurring in younger patients[33,35]." Then Covid-19 adds an even greater strength to the call for action on these inequalities in the new policies which must inevitably emerge following this pandemic.

Arachidonic and docosahexaenoic acids have been known since the 1960s as major constituents of cell membranes including the brain with deficiency leading to cognitive and visual impairment[25-27]. These membrane constituents exhibit anti-viral, immune, anti-inflammatory, blood pressure control and resolvin activity making the case for examining their potential for therapy for Covid-19.

We have published a critique of this view explaining the pivotal role of lipid membranes, with their response to the variations of environmental and chemical diversity involved in the origin of multicellular life. The lipids provided the structural and functional means for intracellular compartmentalisation and cell specialisation, fundamental to the speciation which occurred at the beginning of air breathing life[36]. That being the case, we considered it important to draw attention to evidence on the lipids since the Covid-19 virus depends on its lipid coat for integrity, access to the cell and replication.

It would also be advisable to re-assess food policy in which essential membrane lipids and the brain, have not been considered. The brain is what makes us human and it is a lipid rich organ. There is little doubt the lipids were significant in shaping the human genome over several million years. With the brain as the key to human success, and predominantly a membrane rich system, these would have featured significantly in shaping the human genome and encephalization over several million years. Departure from such conditions would be predicted to put populations at risk to mental ill-health, the present non-communicable disorders and infection, with males being more at risk than females.

Covid-19 has amongst many revelations has brought to our attention the need to fix the food system. Priority will need to focus on the requirements for the optimum integrity and function of the lipid membranes which are of special relevance to the health of the vascular, immune and nervous systems, all of which are presently under threat.

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See in its Chinese version P52-P54.