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Mevalonate pathway, selenoproteins, redox balance, immune system, Covid-19: Reasoning about connections

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ABSTRACT

It has been proposed that a degraded immune system is (one of) the condition(s) that predispose certain subjects to fatal consequences from infection by SARS-CoV-2. It is unknown whether therapeutic regimens to which these patients may have been subjected to in the months/years preceding the infection could be immunocompromising. Statins are among the most widely prescribed cholesterol-lowering drugs. As competitive inhibitors of HMG-CoA-reductase, the key enzyme of the "mevalonate pathway" through which essential compounds, not only cholesterol, are synthesized, statins decrease the levels of cholesterol, and thus LDLs, as an innate defense mechanism, with controversial results in decreasing mortality from cardiovascular disease. Moreover, statins have pleiotropic, mostly deleterious effects on many cell types, including immune cells. In the attempt to decipher the enigma of SARS-CoV-2 infectivology, the hypothesis should be tested whether the population of subjects who succumbed to Covid-19 may have developed a compromised immunity at sub-clinical levels and have become more susceptible to fatal consequences from SARS-Cov-2 infection due to statin therapy.

The hypothesis

It has been suggested that the presence of a degraded immune system is (one of) the condition(s) for the susceptibility of certain predisposed subjects, usually the elderly and those presenting with various co-morbidities, to infection by SARS-CoV-2 and its often fatal consequences. But a significant number of young and otherwise apparently healthy subjects has succumbed, and still is succumbing, to Covid-19. Immunodepression has been linked to several possible environmental factors, such as pollution, electromagnetic fields, global warming, but also to drug induced side effects, such as in oncologic patients on chemotherapy. No attempts have been made, however, to carry out an anamnestic evaluation of the subjects, especially the younger ones, who have died from the consequences of Covid-19. In particular it is unknown whether a weakened immune system could be the result of possible adverse effects from therapeutic regimens to which these patients may have been subjected to in the months/years preceding the infection.

Several drugs have been considered as potential factors that predispose (anti-hypertensive, in particular angiotensin II receptor blockers, mineralocorticoid-receptor antagonists, anti-diabetics) or protect (hydroxychloroquine, corticosteroids) from SARS-CoV-2 infection. However, to the best of our knowledge, no systematic studies have been carried out to evaluate the role played by one family of drugs that has been largely prescribed to the general population over the past couple of decades: the statins. A couple of studies have indeed been published that exclude a statistically significant correlation between Covid-19 outcome and statin routine treatment of patients, but no data on compliance, or cholesterol levels were provided [1,2]. One of the articles has been retracted by the authors almost immediately [1].

Statins

Statins are cholesterol-lowering drugs that act as competitive inhibitors of the enzyme β-Hydroxy-β-Methyl-Glutaryl-Coenzyme-A (HMG-CoA)-reductase, the key enzyme of the "mevalonate pathway". Starting from acetic acid as the building block, this pathway leads to the biosynthesis of isoprenic units, which are in turn assembled to produce such various and essential compounds for both plant and animal cells: dolichol, coenzyme Q, isopentenyl for the modification of tRNAs, farnesyl and geranyl–geranyl for the prenylation of proteins, rubber, plant hormones, phytol chain of chlorophyll, carotenoids, vitamin A, vitamin E, vitamin K, vitamin D, bile acids, steroid hormones and cholesterol. Since HMG-CoA reductase is at the very root of the pathway, its inhibition will prevent the production of not only cholesterol, but also of all the essential compounds listed above. The theory enforcing

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cholesterol-lowering therapies holds that high levels of serum cholesterol, in the form of low density lipoproteins (LDL), are positively correlated with the prevalence of cardiovascular disease and mortality from myocardial infarction and stroke. However, *meta*-analyses of the outcome of several clinical trials have revealed that the correlation between cholesterol levels and mortality is either non-existing or inverse: the lower the cholesterol levels the higher the mortality from all causes, especially those related to infection [3–6]. Furthermore, the levels of LDL cholesterol are inversely associated with longevity in the elderly [5], and low serum cholesterol is even a negative prognostic factor in patients with advanced heart failure, independent from lipid-lowering therapy [7].

LDL cholesterol as part of the innate immunity

The role of lipoproteins as first line defense against microbial infection is well established [8,9]. Prolonged infection with hepatitis B virus has been show to correlate with low blood cholesterol levels and cancer [10], and hypocholesterolemic men have significantly fewer circulating lymphocytes, total T cells and $CD8^+$ cells compared with hypercholesterolemic subjects [11]. In spite of this evidence, the prevailing theory has not been overturned, and statins are still widely prescribed for the "treatment of blood cholesterol" [12]. Indeed, although statins are ineffective in the secondary prevention of cardiovascular events, they appear to be beneficial in the primary prevention of mortality from myocardial infarction. However, the benefit is very modest, as one hundred subjects need to be treated to prevent one single infarction–related casualty [3]. Moreover, this efficacy appears to be related to one of the multiple pleiotropic effects of statins (see below), i.e. an anti-inflammatory effect, rather than a cholesterol-lowering action.

Adverse effects of statins

A number of different cell types can be targeted by the adverse effects of statins, the best known being the skeletal muscle cell. Severe rhabdomyolysis, leading to more than 30 deaths, was reported in 2001 for subjects on treatment with "first generation" statins [13]. All muscle cells, including the myocardium, are especially dependent on mitochondrial respiration for the production of ATP. Coenzyme Q is an essential component of the electron transport chain in the inner mitochondrial membrane and it is synthesized in the mevalonate pathway. One of the most diffusely reported adverse effects of "new generation" statins is myopathy, which is linked to mitochondrial damage likely resulting from deficiency of Coenzyme Q. Not surprisingly, Coenzyme Q supplementation has been found to ameliorate myopathy in subjects on statins [14]. Deleterious side-effects of statins on the central and peripheral nervous systems, including cognitive disorders have also been reported [3].

Because statins inhibit the biosynthesis of substances that are required for the post-translational modification of proteins (and the maturation of tRNAs, see below), virtually every cellular metabolic and signaling pathway may be affected. Thus, statins exert a general inhibitory action on immune cells, probably by interfering with prenylation of G proteins: growth, proliferation, adhesiveness and chemotaxis are inhibited in monocytes [15]. Lymphoid cell function is suppressed by statins in vitro, although the mechanism has not been characterized [16]. Given their depressive action on immune cells, statins have been proposed as immunomodulators with milder effects than the conventional immunosuppressive drugs [17]. It can be concluded that statin therapy may contribute to generalized immunosuppression.

Redox balance and statins

Less investigated is the impact of statins on redox metabolism. An important contribution to the redox balance in cells and tissues comes from selenoproteins, which contain one or more selenocysteine (Sec) residues in their sequence. The majority of seleoproteins are selenoenzymes, as the Sec residue(s) are located in the catalytic site, with antioxidant and oxidative damage-repairing activities. The human selenoproteome comprises 25 different selenoproteins [18]. The best characterized are glutathione peroxidases, thioredoxin reductases, iodothyronine deiodinases, and SelR, or methionine-*R*-sulfoxide Reductase 1 (MsrB1) which reduces the L-methionine-*R*-sulfoxide and has an important role in repairing proteins that have lost function because of oxidation of L-methionine residues. Of the less characterized selenoproteins, some are molecular chaperones in the endoplasmic reticulum, others (SelN) are important for muscle function, as their mutation is associated with muscular disease [19]. For a third class of all selenoproteins the role is still unknown [18]. Glutathione peroxidases are antioxidant enzymes in plasma and blood cells. MsrB1 is highly expressed in neutrophils [20]. All selenoproteins are synthesized through a mechanism of translational recoding of the STOP codon TGA (UGA in the messenger) as a codon for Sec insertion. Key factor in this mechanism is the special $tRNA^{Sec}$, which must carry an isopentenyladenosine at position 37 for being functional [21]. The isopentenyl moiety required for this modification is produced in the mevalonate pathway, hence the link with a potential inhibitory effect of statins on selenoprotein expression [22].

Increased oxidative stress is one of the factors that explain statin-induced myopathy. This effect has been until now mainly linked to decreased levels of Coenzyme Q and associated increased production of reactive oxygen species in the mitochondrion [23]. However, a contribution of selenoproteins downregulation to the generation of a statin-induced pro-oxidant state in muscle and other tissues could be conceived, although it has not been evaluated so far.

Pro- or anti-inflammatory effects of statins?

As statins have been claimed to have anti-inflammatory effects, it may seem contradictory that they could contribute to the hyper-inflammatory state observed in Covid-19 patients. However, statins interfere with the proper modification of essential G proteins in the signal transduction pathways that control innate immunity. Inhibition of prenylation of Ras-family G-proteins is associated with the generation of a hyper-inflammatory conditions with hyper-production of pro-inflammatory cytokines [24]. Interestingly, mevalonate-kinase-deficiency, a hereditary disorder associated with a defective mevalonate pathway, is typically characterized by an auto-inflammatory state of the patients [24]. Statins may also perturb acquired immunity by altering antigen presentation by antigen-presenting-cells [25].

Evaluation of the hypothesis

It may be concluded that an intact redox balance is essential for white blood cells and that it would be worth investigating whether downregulation of selenoproteins may contribute to compromise leukocyte function in subjects on statin therapy. This study cannot be a retrospective analysis of pre-existing data, because, to the best of our knowledge, no quantification of selenoprotein activity has ever been carried out in vivo in subjects on statin treatment compared to normal subjects.

A recent nutritional study reports on a beneficial effect of selenium supplementation on markers of muscle damage in subjects on statin therapy [26]. Selenoprotein expression levels were not changed, except for an increase in glutathione peroxidase activity, which correlated with a decrease in serum creatine kinase activity, in subject supplemented with selenium. However, the study lacked a control of normal subjects not on statins. Therefore, until now it is not known how the modulation of the mevalonate pathway activity impacts on the levels and availability of the various intermediates produced in the pathway

and in particular on selenoprotein activity. Also lacking is the information whether hypercholesterolemia is associated with increased levels of mevalonate pathway intermediates. Therefore, this hypothesis could only be tested within an “ad hoc” research project, possibly in a placebo controlled, double blind type of study.

A second prediction of the hypothesis could be tested retrospectively, as discussed below. HMG-CoA reductase as well as most enzymes for sterol biosynthesis are all integral membrane proteins in the endoplasmic reticulum of eukaryotic cells. All cells require cholesterol and most cells actively synthesize it as an essential structural constituent of the plasma membrane. For the purpose of replicating, a virus heavily engages the host cell’s molecular machinery for protein synthesis and vesicular trafficking and in this process it deranges the cell’s metabolism. It is expected that any cellular reaction that takes place at the level of the endoplasmic reticulum membrane, like the mevalonate pathway, will be affected by the tremendous burden that an actively replicating virus poses on the intracellular membranous compartments. This view seems to be supported by a report revealing a sharp decrease in neutrophil, lymphocyte and cholesterol levels in Covid-19 patients [27]. Thus, subjects with already low LDL levels and possibly weakened leukocyte function because of statin treatment would be even more susceptible to infection and its fatal consequences.

This prediction of the hypothesis could be tested by retrospectively evaluating whether a correlation exists between the cholesterol levels of subjects infected by SARS-CoV-2 and the severity of the consequences suffered with the progression of the disease.

Consequences of the hypothesis and discussion

The long list of harmful effects that statins exert at all levels of biochemical cellular processes should be sufficient to outweigh the minor potential benefits that these drugs may show in preventing cardiovascular disease. The minimal benefit in reducing the absolute risk of myocardial infarction by one mere percent point may be linked to statins’ an anti-inflammatory action, which, however, is associated with a plethora of adverse effects that include dysregulation of immune cells. Therefore, the suggestion that statins should be used for the prevention of Covid-19 is questionable [28,29].

By decreasing the levels of LDLs as an innate defense mechanism against pathogens and by unleashing the power of a drug that acts at multiple basic cellular levels with deleterious effects, we may have reared a population of subjects who have over time developed a compromised immune system. A new perspective ad alternative approaches are mostly wanted to address an issue of such general interest as a global infective pandemic. Serious attempts to decipher the enigma of the SARS-CoV-2 infectivology must certainly include the analysis of factors that could compromise the immune system, among which statin therapy has to be included.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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