NOVEL CORONAVIRUS: HYPOTHESIS OF TREATMENT WITH SIRT1 INHIBITORS

To date, it is known that the **Novel Coronavirus penetrates** into the host via the **enzyme converting receptor for angiotensin II (ACE2),** by **binding** to **glycoprotein S**, with some differences from what happens with Sars-Cov.[1]

From here, you can draw up a **list of interventions** to **reduce the expression of ACE2 activity**, in order to avoid (in whole or in part) the entry of the virus into the subject under attack, but not only. It is also possible to **reduce the ability of the virus to reproduce** and **lower its endoribonucleic activity**. So, let us see what can be done.

ACE2 DIRECT INHIBITORS

We assume that ACE inhibitors (Lisinopril, Quinapril, Captopril) don't reduce ACE2 activity, despite being structurally related and traceable in the same organs, ACE2 has opposite biological effects (vasodilatation, bronchodilatation, activity to compensate for physical stresses, as some particular conditions, like hypoxia); some direct ACE2 antagonists are:

- **The small molecule MLN-4760-B, its isomeric MILN-4760, much more selective and effective;**
- **DX600 peptide (and DX-512) having a nanomolar affinity for ACE2, much more than for ACE (almost null), competitive and non-competitive inhibition.**

The effectiveness and selectivity between these two elements are concentration-related, but at the concentration of 10μM, MLN-4760 was found to have a better activity profile.[2]

SIRTUINE INHIBITION

There is also the possibility to act indirectly, through **a Sirtuine group protein, 7 enzymes NAD+ dependent**, know as **SIRT1**, This is what makes it an **interesting target** in the search for a cure for the CoVid -19 (but also for the Sars-Cov and Mers-Cov):

1. Expression of ACE2 activity varies with binding to SIRT1 protein, so **inhibiting SIRT1, we lowering ACE2 activity;**[3]

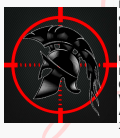
2. Sirtuine are located in the **cellular nucleus** (SIRT1, SIRT6 and SIRT7), in the **cytoplasm** (SIRT2), or in the **mitochondria** (SIRT3, SIRT4 and SIRT5) and are involved in many **cellular functions**, such as metabolism, the cell cycle, l'apoptosis, DNA repair, etc. Recent studies have found that sirtuine **may also have enzymatic functions**. They are sensors of changes in the intra- and extracellular environment, generally involved in maintaining human health, but think, for example, of the **Tat protein** of the **HIV virus**: its **activity is regulated by SIRT1**, whose activity of deacetylase, vice versa is inhibited by the protein Tat. The **transcription** of HIV **is regulated by SIRT1**, by means of **Tat deacetylase**. **SIRT1 preserves the defenses of the virus, throughout its evolution**, allowing the **recycling of the protein tat**, which **binds to TAR**, and the continuous **prolongation of the mRNA transcription**;[4]

3. **SIRT1 inhibition** (and sometimes even SIRT2) by minor **changes to siRNA**, is known to cause the **decrease in replication of additional viruses**: flu strains, VSV (Vesicular Stomatitis Virus), KSHV (Kaposi's Sarcoma-associated Herpesvirus), Hepatitis B, HCMV, adenovirus, polyomavirus and in some diseases counteract: some types of cancer and Huntington's chorea, sometimes in combination with antivirals, for the best results;

4. Among the various other viruses that respond by **slowing their growth**, there is just **Mers-Cov**. It has been observed that **SIR2** (SIRT1 is the human correspondent) acts as the **proviral of Mers-Cov** in the **yeast**, due to interactions between ORF4a and eukaryotic cells. **YDL042C/SIR2** yeast gene is a **suppressor of ORF4a** function. **When SIRT1 is inhibited** by either chemical or genetic manipulation, **there is a reduction of MERS-CoV replication**. Moreover, **ORF4a inhibited SIRT1-mediated modulation of NF-κB signaling**, demonstrating a functional **link between ORF4a and SIRT1 in mammalian cells**. It been identified a functional link between the MERS-CoV ORF4a proteins and the YDL042C/SIR2 yeast gene.[5]

5. **VSV-SARS-St19 infection is mediated by SARS-CoV-S protein in an ACE2-dependent manner**. VSV-SARS-St19 will be useful for analyzing the function of SARS-CoV-S protein and for developing rapid methods of detecting neutralizing **antibodies** specific for **SARS-CoV** infection. **SIRT1 inhibitors stop the growth of VSV**, since that **cells' apoptotic response is reduced in cells affected by VSV**.[6]

I believe that the use of **SIRT1/SIRT2 inhibitors** in the **treatment of the Novel Coronavirus** CoVid-19 **should be seriously evaluated**, as there is much **evidence that it may slow down growth, if not completely halt it**.



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