SARS-COV-2 and COVID-19: from RESEARCH to PREVENTION

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State of the art

This study was developed together with a network of physicians, scientists, researchers, and university professors who have decided to use their skills and studies conducted in recent years to better understand the biochemical mechanisms of activation, silencing, and replication of *Betacoronaviruses* (MERS-CoV, SARS-CoV, SARS-CoV-2).

Several studies conducted in recent years have made it possible to detect that *Betacoronaviruses* are among the main pathogens that cause epidemics of respiratory diseases, and belong to the large family of single-stranded RNA viruses (ssRNA(+) that can be isolated in different animal species including camels, cattle and bats.

Oxidative stress and **cellular defense mechanisms** are the basis of the investigations I carried out, including the **DNA methylation** that intervenes, decisively, in the activation and replication processes of viruses.

DNA methylation is an epigenetic mechanism used by cells to manage gene expression. Methylation refers to the process of adding the methyl (CH3) group to specific regions of DNA. Although DNA methylation has been observed since the 1950s, its mechanism and role in viral and bacterial infections are still under investigation. In 1953, the first evidence of DNA methylation was found in bacteria during phage infection. In this case, DNA methylation is aimed at protecting the bacterial DNA from the phage's foreign genetic material. If this Methylation process does not work at its best, these portions of foreign DNA could lead to **very serious and dangerous diseases**.

Research hypothesis

My scientific hypothesis is that SARS-CoV-2 is activated due to **the depletion of reduced glutathione** and the consequent catalase inhibition at the intracellular level, which occurs in an organism in which the cellular redox homeostasis is in imbalance, i.e. in subjects in **permanent oxidative stress**. The imbalance of the redox system towards an oxidation state and a malfunctioning of methylation activates the virus and its replication, causing inflammation and an aggravation of the patient's health, to the point of causing death.

The imbalance towards the oxidant phase (the oxidants are greater than the reducing agents) in subjects showing high homocysteine levels (hyperhomocysteinemia) causes the arrest **(inhibition) of catalase** and the (intracellular) reduced **glutathione depletion**. This imbalance in the system of the oxidoreductase group, secondary oxidation reactions similar to those catalyzed by peroxidase, causes a malfunction of methylation and the consequent replication of the virus, which activates a chronic inflammatory state due to the peroxides released by our immune system, which fails to fight the virus and releases harmful elements that lead to the collapse of the organism. The release of peroxides can lead to the Multiple Organ Dysfunction Syndrome and death from cardiac arrest.

My hypothesis is that the malfunction of the methylation process depends on a malfunction of the methyl (CH3) groups, since these methyl groups in case of correct functioning in humans, according to my studies, do not allow the replication of the virus. They use DNA methylation as a mechanism to escape host immunity and ensure effective viral replication and persistence.

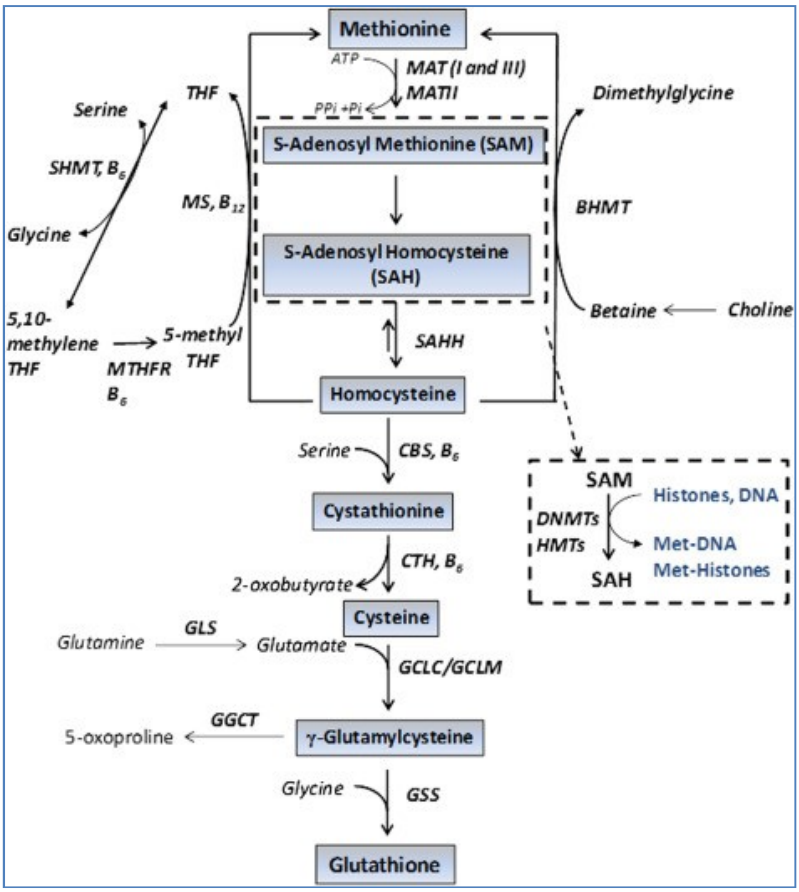

Figure 1: Metabolic cycle of Homocysteine and Glutathione

The strategic objectives for blocking virus replication then become the following:

- rebalance the redox system and bring the cell back to its normal state from the state of oxidative stress, with the aim of being able to cope with conventional therapies in the field of oncology and infectious diseases under optimum conditions through the use of therapeutic protocols dedicated to rebalancing the redox system and protocols for laboratory diagnosis of the oxidative stress state;
- suggest integrated therapy for the treatment of infection due to the COVID-19 virus: the C.R.A.Pu. therapy (Complementary Reducing Anti-degenerative Therapy by Puccio);
- define a preventive prophylaxis for the infection caused by the COVID-19 virus.

C.R.A.Pu. Therapy

This intervention aims to immediately negativise individuals who have the following symptoms: dyspnoea, high fever with a cough, before the virus is activated and replicates.

The C.R.A.Pu. Therapy constist of drips for clinical phenotypes with acute respiratory distress syndrome (ARDS) in mechanical ventilation and an oral part for positive asymptomatic clinical phenotypes.

A central role in the defence mechanism of cellular structures in general, and of erythrocytes in particular, against free radicals, peroxides and oxidising agents in general, is played by the glutathione-ascorbate system, which acts as a rapid donor of H+ ions and electrons. This reduction system, resulting from the cooperation of GSH with the oxidation-reduction activity of ascorbate, in normal conditions is continuously regenerated through a sequence of reactions involving two enzymes: glutathione peroxidase (a) and glutathione reductase (b).

THEREFORE, THE CELL DEFENSE MECHANISM AGAINST OXIDIZING AGENTS IS IN GENERAL SCHEMATISABLE AS FOLLOWS:

1) Ascorbate + oxidizing agent → dehydroascorbate + H_2O_2
2) Dehydroascorbate + 2 GSH → Ascorbate + GSSG
3) H_2O_2 +2GSH →2 H_2O+ GSSG
4) GSSG + NADPH + H^+→2GSH + $NADP^+$

The unavailability of GSH is in turn directly responsible for important alterations in the red blood cell, mainly concerning the integrity of the membrane and haemoglobin. The liver and muscles are the most important tissues transferring reduced Glutathione to the plasma. The lack of GSH in erythocytes profoundly alters various essential metabolic processes and is also responsible for a type of haemolysis, so restoring this important function requires a:

Phleboclysis - prepare an IV with the following items:

- No. 1 0.9% Physiological solution - 500ml;
- No. 3 vials of GSH - 600 mg;
- No. 2 vials of N-acetylcysteine - 300 mg;
- No. 1 vial of ascorbic acid - 1 g, which must be increased up to 4 grams depending on the neutrophils or the high LDH value, to block peroxides and avoid damage to the cardiac muscle.

It is necessary to modify the treatment on the basis of certain parameters of the patient, which will be monitored before the start of therapy and in the intermediate phase of administration in order to intervene on the dosage and the integration of other elements.

As a first step, a patient status evaluation form should be prepared. In addition, we recommend the following tests: *Blood count (Absolute neutrophil count), Serum protein electrophoresis, Procalcitonin, LDH, Fibrinogen, D-dimer, Ferritin, YGT, PCR, Vitamin D, Homocysteine, Calcium, PTH, B9, B12*. In more severely affected subjects, the levels of altered intestinal permeability and the consequent activation of inflammatory pathologies could be investigated by checking the (high) parameters of *IL-6, IL-17 and IL-22*, and if possible *Occludin, Zonulin and Calprotectin* as well as *LPS*, to name but a few biomarkers.

Oral administration - the oral treatment to be followed is shown below

It can also be integrated in the case of: ***hyperhomocysteinemia*** and vitamin D deficiency; in case the patient is found to be positive; for therapy to be given in addition to medication. This prevents the virus from replicating and increasing its viral load to cause multi-organ damage. The decrease in temperature and increase in saturation will let us know that we are blocking viral replication:

* Vitamin D at least 10,000 units per day (15,000 for over-70s) and, after 5 hours, vitamin K2 in a 10:1 ratio;

- Betaine anhydrous (Trimethylglycine) - has been approved by the NDA (New Drug Application), the recommended dose is one gram per day, in Italy, the Ministry of Health has deemed it appropriate to establish a maximum daily dose of 250 mg per day (optimal dose for us amounts to 500mg);
- B6 - 1.5 mg per day;
- B9 (folic acid) - 400 mcg per day;
- NAC – 600 mg per day (if not integrated into a drip) forms cysteine in the body to activate the glutathione cycle.
- B12 - 33 mcg per day.

If homocysteine is not lowering (MTHFR mutation), we intervene with methylfolate (calcium mefolinate 15 mg per day)

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Preventive Prophylaxis

For prophylaxis, it is essential to carry out some blood tests that can be easily prescribed by the general practitioner. The latter are listed below:

- plasma homocysteine analysis;
- vitamin D analysis;

In case of high homocysteine values (concentration > 13 ng/mL) and low Vitamin D values (concentration < 30 mcg/mL) it will be necessary to undergo the oral administration of the C.R.A.Pu Therapy.

Conclusions

Understanding the mechanisms of immune evasion in viruses and bacteria has attracted the interest of many scientists. This work proposes an innovative diagnostic study (clinical trial) that may provide us with useful insights into the methylation systems activated by viruses and in bacteria. We are convinced that the high morbidity of SARS-CoV-2 is linked to its extreme mutagenicity, which could be caused by the binding of the virus to particular bacteria in the body, and for this reason we suggest the C.R.A.Pu. Therapy alongside effective therapies to treat the disease. We hope to monitor the patient's response to the therapy through specific diagnostic tests, but above all we hope to create a clinical trial that could contribute to studies that are still preliminary studies.

Signatories:

- *Dr Santi Scola, MD, Hematologist, Clinical Pathologist, Epidemiologist, member of the SIPMel board of directors. Founder of sez. Siciliana Tecnici di laboratorio dei Medici e dei Biologi and scientific consultant of the Associazione Emmanuele.*

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- *Dr Simone Cristoni, ISB - Ion Source & Biotechnologies SRL*
- *Dr Massimo Romano, MD, Cardiologist and internist of Federico II di Napoli.*

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