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Development of Novel Strategies Against COVID-19

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ABOUT THE STUDY

The full genome structures of the coronaviruses have been decoded [1-4]. On the other hand, taking in consideration the proved role of ACE2 as the main target of SARS-CoV-2/COVID-19, as well as of the other members, belonging to *Coronaviridae* family (as the agents, causing SARS and MERS) [5,6]. As an integral part in the activation and induction of a conformational change of the S-protein–ACE2 receptor complex, which allows the further process of fusion between the virus particle and the host cell, has been proved the enzyme serine protease (TMPRSS2) [7,8]. By penetration in the cell through the cellular receptor for this enzyme, the negative influence of these viruses, but even of their components, on the enzyme functions should also be taken in consideration as underlining in many symptoms of this infection, including injures in the functions of many important anatomic organs [9]. Furthermore, the role of Renin–Angiotensin–Aldosterone System (RAAS) has been proved as key in the regulation of the systemic blood pressure and renal function [6,8,10] Despite of the key importance the immunity, the activated immune reaction, including by vaccines, could cause unwished effects, for instance in cases as allergies, auto-immune diseases and disorders, as well as cardio-vascular pathologies. Toxic side effects of the chemical anti-viral preparations should also be taken in consideration.

In this connection, the main goal is directed to suppression of the cellular penetration and/or replication of SARS-CoV-2/COVID-19, both *in vitro* and *in vivo*. For this goal, specific siRNAs against the virus gene, coding viral Spike (S) protein, as well as of molecular vaccines against other virus protein(s), should be developed and tested.

Theoretical orientation

In vitro-incubated cells should be inoculated with viral strain with RNA-genome (if is possible, belonging to *Coronaviridae* family), which should then be treated with appropriate siRNAs against the virus gene, coding viral S protein, necessary about viral penetration in the cell. Molecular vaccines against other virus protein(s) should also be designed. Subsequent evaluation on the *in vivo*-influence of the tested siRNAs against virus S protein and molecular vaccines against other viral protein(s) on appropriate experimental animals, both non-infected controls and previously infected with the same RNA-viral strain, should be performed.

Discussion

By application of the described methods was achieved successful suppression and/or activation of cellular oncogenes and tumor-suppressor genes in normal and malignant cellular types [11, 12], by taking in consideration respective literature sources [13-15]. Additionally, in *in vitro*-and *in vivo*-conditions was generated adequate immune reaction against malignant transformation changes, but also protection against degenerative changes. Furthermore, in this way, possibility for production of membrane receptor glycoproteins by non-myeloid and non-lymphoid cellular types was proved in appropriate conditions (as for instance, presence of viruses or virus antigens, of malignant cells/antigens, appropriate immunomodulators, etc.), which was in agreement with the literature findings [16-18]. Also, the results obtained suggested a possibility besides transfer of nucleotide (DNA-and/or RNA-) sequences from virions to cells, also in the opposite direction – from cells to viral particles. These data could explain some cases of protection by various internal and external factors against viral diseases [19-22]. Analogically, a possibility for production of immunoglobulins/antibodies by non-lymphoid types of cells, tissues and organs was established [11, 12, 23-29], which was also in confirmation with the literature data in this direction [30-32]. One of the explanations was connected with existence of low-differentiated stem-like cellular sub-populations, which are able to differentiate in various directions. According to another hypothesis, some cell-produced proteins could act as antibodies or antibody domains to specific bio-molecules [16,30-32]. However, because the so produced immunoglobulins/antibodies are out of the germinate centers of the lymphoid tissues and organs, their functions should be controlled for escape of chronic inflammatory processes, which could lead to malignant transformation or to degenerative changes. As key in this control is proved the role of small ions and molecules by indirect and/or direct participation in various intra-and extra-cellular inter-molecular interactions [33, 34].

Future perspectives

Further intra-and extra-cellular interactions between different biological molecules (protein-protein, protein-RNA, protein-DNA, protein-lipid, protein-carbohydrate, DNA-DNA, DNA-RNA, RNA-RNA, DNA-DNA, etc.), underlining these processes, should be performed. CRISPR/Cas systems as universal mechanisms, responsible about normal/non-malignant cellular differentiation, adequate immune reaction, but also of cellular ageing and death, should be investigated. After performance of all steps, described above, evaluation on the *in vivo*-influence of the tested siRNAs against virus S protein and molecular vaccines against other viral protein(s) on appropriate immunodeficiency rodents as NOD or SCID mice, among which should be available sub-groups, previously infected with the same RNA-virus strain.

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