Physiol. Res. 70 (Suppl. 2): S123-S124, 2021

Guest Editors Introductory Words

Dear readers,

Starting in early 2020, Coronavirus pandemy impacted hundreds of millions people worldwide. This was reflected by enormous effort of physicians, scientists and politicians to fight against this threat. Many more or less severe measures were imposed to stop uncontrolled spreading of the virus, and in a relative short time an impressive amount of knowledge was collected about the virus, its action and possible ways of treatment. In spite of pessimistic prognosis the first effective vaccines were developed as early as within one year and immediately applied in large populations.

In this volume we attempted to bring a representative collection of reviews mostly from Czech and Slovak authors, embracing various fields of physiology addressing the COVID-19 pandemic. It concerns mostly endocrinology, immunology, molecular biology and genetics and clinical experience.

Intimate relation between COVID-19 and endocrinology demonstrates first of all the link between renin-angiotensin system (RAS), responsible for regulation of electrolyte homeostasis, and the role of the homologue of angiotensin converting enzyme (ACE), the protease ACE2, serving as a receptor for COVID-19 spike protein. Binding of the latter to the receptor leads to fusion with the host membrane followed by entry of the pathogen into the cells. The binding of coronavirus downregulates ACE2 (Máčová *et al.*, this issue) A detailed review of the molecular mechanisms acting from the binding of the virus to its receptor and following events until the replication of the virus in the host is provided in the review of Zlacká *et al.* (this issue). ACE2 is thus considered as a therapeutic target.

Severity of COVID-19 infection is dependent on age and affects more men (Máčová *et al.*, this issue). It is therefore not surprising that it is related to the changes of steroid hormonal status. Recent findings point to the role of androgens. Generally, male sex hormones belong to anti-inflammatory agents and may thus protect from cytokine storm, typical for affected individuals. Androgens (as well as estrogens) possess anabolic properties which may moderate infection. On the other hand, the study of molecular events behind the entry of the COVID-19 into the host cells revealed a number of co-operating proteins among which a key role plays the transmembrane protease serine 2 (TMPRSS2), which is needed to cleave the spike protein and assist in membrane fusion, the expression of which is increased by androgens *via* androgen receptor activation (Stárka and Dušková, this issue, Knížatová *et al.*, this issue). All these actions are genomic, but recent research of the role of androgens revealed that the latter possess also rapid, non-genomic response, as demonstrated that they are not inhibited by both transcription and translation inhibitors (actinomycin, cycloxeximide) as well as androgen receptors blockers (flutamide). Besides classical androgens testosterone, dihydrotestosterone and dehydroepiandrosterone, a particular function has the beta-epimer of dihydrotestosterone (5β-DHT), completely inactive to intracellular androgen receptors (Perusquía, this issue). Further studies may be expected of elucidation the role of the respective enzyme steroid 5β-reductase. In conclusion, low androgen levels as well as hyperandrogenemia are risk factors for development and severity of COVID-19 disease.

Large number of studies have been dealing with genetic background of COVID-19 prevalence susceptibility and mortality, with respect to geographical and interethnic differences. The impressive number of genes and their polymorphism were screened to find out genetic markers, enabling to predict the susceptibility to infection and its severeness. This issue was briefly reviewed by Hubáček (this issue). Many of studies were based on *in silico* data, which need not reflect the real situation. The effort was focused first of all on the key players in the mechanism of pathogen entry into the host cell: as ACE, ACE2, TMPRSS2 and a number of other genes which may participate in the infection process. It contained genes encoding chemokines, cytokines and other factors with potential impacts on the infection. It included also vitamin D receptor (VDR), with respect to the known fact that vitamin D deficiency is much more common within the groups who are at highest risk of severe COVID-19. Surprisingly, none of ACE2 variations have been directly associated with COVID-19 susceptibility or severity, while significant association of severity and mortality from COVID was found with the genes inherited from Neanderthals. Attention was also paid to susceptibility of bearers of individual blood groups (AB0) and their characteristic genes. Increased risk of COVID-19 is associated with blood group A and with the APOE4

allele. The author concluded that only five genetic determinants of SARS-CoV-2 infection and COVID-19 severity seems to have consistent effects, of which only ACE is directly involved in the infection mechanisms.

The genetics is also addressed in a specialized contribution of Croatian authors on the receptor for proinflammatory chemokines CCR5, involved in host responses to viruses. The CCR5 Δ32 minor allele is an interesting variant, given the role of CCR5 in some viral infections, particularly HIV-1. A significant negative correlation was found between CCR5-Δ32 allele frequency and COVID-19 case counts and deaths in Europe (Starčević Čizmarević *et al.*, this issue).

The effect of COVID-19 disease is complex and affects strongly innate as well as adaptive immune system. Infection in severe cases leads to acute tissue damage due to a pathological immune response. One of the characteristics of impaired cellular immunity occurring in COVID-19 patients is "T cell exhaustion" concerning mostly effector T cells, consisting of a reduced ability to secrete cytokines and an increased expression of inhibitory receptors. One of the features of COVID-19 is the upregulation of such inhibitory receptors as e.g. programmed cell death proteins. This aspect is addressed by Barnová *et al.* (this issue) who focused the attention on the role of so called inhibitory checkpoint molecules which regulate the immune system. The role of nine of these proteins is discussed in the light of using them as therapeutic target.

The activity of innate and adaptive immune system differs between children and adults, the former being stronger in the youngest groups. Suppressed adaptive immunity and an impaired innate immune response is seen in adult patients with severe infections but not in children, who, in addition, do not have so many comorbidities. The most endangered population are seniors due to progressive immunosenescence. Kapustová *et al.* (this issue) describe the main differences in the mechanism of covid infection in children and adults. It is shown that differences between children and adults consist of the expression of viral receptors required for viral entry, different innate immune response, diverse cytokine production, and different mechanisms of adaptive immune response.

This supplement also deals with clinical, namely pneumological problematic. Čalkovská *et al.* (this issue) review the role of lung surfactant and its changes in COVID infection. The lungs and namely alveolar ATII cells containing ACE2 receptor as well as cooperating TMPRSS2 and are thus the primer site of infect entry. Their impairment is the main clinical feature of severe COVID-19 infection. This usually include injury of the alveolar-capillary barrier, lung edema, inflammation, ineffective gas exchange, impaired lung mechanics and reduced oxygenation. Lung surfactant, a unique composition of phospholipids, proteins and other active molecules, which lines the inner surface of the alveoli and small airways, serves as an interface between gas and liquid and thus plays a key role in the physiology of the respiratory system. Not negligible are its multiple immune, mostly defensive functions which attracted the attention during the COVID-19 pandemic. Exogenous surfactant treatment in COVID-19 patients is also discussed.

Richard Hampl and Marie Bičíková