of placental AhRs by CoV can trigger release of cytokines by placenta and fetus leading to activation of cyclooxygenase-2 (COX2) in trophoblasts and amniotic epithelial cells and release of prostaglandins such as PGE2 and PGF2α (Li et al., 2015). We hypothesize that if the activation of AhRs during CoV infection persists, activation of AhR-COX2/PG pathway may, in sensitive individuals, initiate myometrial contractions and lead to preterm birth (Li et al., 2015).

6. Multiple organ injury may be AhR dependent

Protracted infection with SARS-CoV-2 may lead to injuries of multiple organs including the lung, heart, kidney, and liver (Zheng, Ma, Zhang, & Xie, 2020). CoV infected children can also develop such multiple organ injuries (Cui et al., 2020). During early infection, translocation of SARS-CoV-2/ACE-2 complexes into the lung alveolar epithelial cells, or other organ epithelial cells, and massive intracellular viral replication (Cava et al., 2020) may lead to cell death (Chen, Li, Chen, Feng, & Xiong, 2020) due to activation of AhRs leading to increased expression of CYP1 family genes such as CYP1A1, CYP1B1, and CYP1A2. This results in initiation of apoptosis via activation of caspases dependent pathways, and to ACE-2 down-regulation, which after release of viruses from infected host cells offers a new entry establishing a multiple positive feedback loop accelerating infection (Abassi, Assady, Khoury, & Heyman, 2020). During late phase of the disease, cytokine elevation related to persistent activation of AhRs by CoV, can also induce tissue injury in diverse organs, and contribute to worsening of clinical manifestations and disease outcomes. Cardiomyocytes exposed to TCDD, an AhR agonist, also respond with increasing CYP1A1 mRNA and protein expression in an AhR dependent manner suggesting activation of the AhR/CYP1A1 signaling pathway (Zhou et al., 2017). Therefore, we hypothesize, that the AhR/CYP1 signaling pathway may be activated by CoV in organs undergoing tissue injuries during both early and late stages of disease, and that elevated cytokines such as IL-6, IL-8 or IL-1ß (Leisman, Deutschman, & Legrand, 2020) may activate diverse signal cascades causing and accelerating tissue injury. One such mechanism involves the Notch-AhR-IL22 pathway regulating tissue homeostasis (Weidenbusch et al., 2017). In macrophages, Notch signaling enables production of

IL-6, which in turn amplifies Notch-dependent signaling establishing another positive feedback loop accelerating synthesis of IL-6 and perpetuating the Notch-AhR-IL-22 signaling pathway (Weidenbusch et al., 2017). If the inflammatory deluge due to cytokine elevation persists, multiple positive feedback loops become activated whereas the inhibitory feedback loops become gradually inactive. Then the intensity of AhR activation may further increase and tissue damage may occur in different organs. In addition, AhR controls organ homeostasis by governing epithelial cell networks such as intestinal, alveolar, bronchial, or tubular, providing a barrier against toxins and pathogens, by supporting their integrity by means of preventing malignant transformation and allowing for their timely renewal (Rothhammer, & Quintana, 2019). In intestine, activation of AhR by IDO1 induced by oxazoles can suppress anti-inflammatory action of IL-10 and lead to inflammation mediated by IL-13 and IFNγ-producing killer T cells (Iyer et al., 2018). Whether such a mechanism can be activated by viral activation of IDO1 or AhR or both, and whether it may be functional in organs other than intestine, is not known.

7. Brain injury may be AhR dependent

Changes in smell and taste perceptions belong to the earliest symptoms indicating viral invasion of the nervous system by CoV in humans (Lechien et al., 2020; Zubair et al., 2020). However, olfactory sensory neurons do not express either ACE-2 or related serine protease TMPRSS2 genes allowing SARS-CoV-2 passage through neuronal membranes (Brann, Tsukahara, Weinreb, Logan, & Datta, 2020). Since CoV including SARS-CoV-2 enter neurons and may induce brain injury in humans (Zhou, Zhang, Wang, & Gao, 2020), and since in transgenic mice lacking ACE-2, SARS-CoV-1 can enter the brain via olfactory bulbs and spread transsynaptically over many days towards interconnected cortical subfields, amygdala, hippocampus, thalamus, midbrain, periaqueductal gray, and pons causing neuronal death (Netland et al., 2008), we suspect an alternative non-ACE-2 dependent entry mechanism allowing neuronal invasion by CoV. When neuronal entry is established, SARS-CoV-2 will activate AhRs, as it does in non-neuronal cell populations, thereby increasing gene expression of the CYP1 family such as CYP1A1, CYP1B1, and CYP1A2 and initiate apoptosis via activation of caspases (Rzemieniec

et al., 2019), resulting in progressive death of neurons and brain injury (Zhou, Zhang, Wang, & Gao, 2020). It is intriguing that mechanisms involving activation of AhR in neurons leading to apoptotic brain injury have been confirmed in experimental models of stroke (Cuartero et al., 2014).

The brain is complex compared to other organs thereby preventing neurotropic viruses from invading it all at once due to morphological organization and cellular diversity, long distances between different neuronal populations, and synaptic traps set between interconnected parts of it. As the silent and slow journey of CoV through the brain towards the respiratory center continues, cell damage accumulating in initially affected neuronal populations can influence sensitivity of next targeted neuronal populations. Since brain injury reported by Netland et al. (2008) in SARS-CoV-1 infected mice was similar to that triggering spontaneous focal seizures in rats (Cavalheiro et al., 1991), we hypothesize that brain injury cumulating over time in infected individuals may lead to silent limbic seizures, or induce seizure threshold changes. It is intriguing, that even overt convulsions can occur in Covid-19 patients (Hepburn et al., 2020) and that careful analyses of cohorts of critically ill patients suffering from Covid-19 are confirming such observations (Roman et al., 2020), which, however, are still rare and require more attention during follow-up studies. Brain stimulation studies in humans indicate that neuronal limbic/paralimbic networks, which are targeted by infection with CoV in mice (Netland et al. 2008), and consist of amygdaloid and hippocampal neuronal networks, drive in humans ictal central apnea by affecting the periaqueductal gray (Lacuey, Hampson, Harper, Miller, & Lhatoo, 2019). The periaqueductal gray is responsible for modulation of pre-Bötzinger complex neurons, which control the eupneic respiratory rhythm (Subramanian, & Holstege, 2013). Since periaqueductal gray is targeted by CoV (Netland et al., 2008) and it may also be affected by a dysfunctional limbic/paralimbic breathing modulation network in humans (Lacuey, Hampson, Harper, Miller, & Lhatoo, 2019), we hypothesize that in critically ill patients CoV may reach the medulla and the pre-Bötzinger complex, which contains respiration regulating cholinergic neurons (Carey, Dunn, & Gaspari, 2013), and contribute to their activation, apnea, and death. Stimulation of the caudal part of the ventrolateral periaqueductal gray in rats inhibits both pre-inspiratory cells and the diaphragm leading to respiratory failure lacking dyspnea (Subramanian

& Holstege, 2013). If CoV reach periaqueductal gray and enter cholinergic neurons in the pre-Bötzinger complex, activation of AhR may also suppress activity of acetylcholinesterase (AChE) in these neurons (Xie et al., 2013) and induce stimulation of effector cells, eventually leading to inhibition of pre-inspiratory cells and apnea.

8. Environment and AhR

Early analyses indicate that exposure to air pollutants may complicate the course of Covid-19 and lead to more severe and lethal outcomes (Domingoa, & Rovira, 2020). Atmospheric particulate matter air pollutants such as polycyclic aromatic hydrocarbons and dioxins, but also nitrogen oxide, ozone, and carbon monoxide have deleterious effects on the respiratory system in humans, and AhR is a target for several of them (O'Driscoll, & Mezrich, 2018). Individuals chronically exposed to such pollutants may be at higher risk of contracting viral infections since AhRs determine innate and adaptive immunity, and govern transcription of xenobiotic metabolizing enzymes such as cytochrome P450 with CYP1A1 and CYP1B1 (Tsatsakis et al., 2020). Since AhR signaling is dependent on multiple proteins, activation of AhRs by urban dust, polycyclic aromatic hydrocarbons, or diesel exhaust may lead to up-regulation of multiple sets of downstream effectors promoting different pathologies and making humans more prone to pathogens including CoV (Tsatsakis et al., 2020).

Another set of issues arises from clinical experience with SARS-CoV-2 indicating that severity of the disease in humans may vary from minimal to critically ill and disease duration from few days to many weeks. Assuming that during clinically active Covid-19 AhRs remain maximally activated poses the question of long-term sequelae of Covid-19, which needs to be addressed by epidemiological studies in survivors. Relevant clues guiding towards answers may arrive from epidemiological studies on human exposure to the Agent Orange contaminated with dioxin TCDD, which is an AhR agonist, pointing to increased prevalence of cancers, endocrine disorders, neurological disorders, pulmonary diseases, and liver cirrhosis (Yi, Hong, Ohrr, & Yi, 2014).

Since CoV persistently activate AhRs, this may lead to up-regulation of multiple sets of downstream effectors resulting in different pathologies (Fig. 2) depending on time after infection, individuals overall state of health, comorbidities, and environmental

factors affecting AhRs. We believe it is therefore appropriate to describe this disease as a systemic AhR activation syndrome (SAAS), which can manifest in an acute (current pandemic), and perhaps later, in a chronic form, in survivors.

9. Dual mechanism of AhR activation: a chance for therapy

Since CoV initially bypass the common IDO1-kynurenine-AhR pathway, factors which activate AhR directly may facilitate infection. Eliminating such factors may be critical for prophylaxis but also for therapy of CoV infections. When CoV enter the human body and symptoms are mild or disease is subclinical (Huang et al., 2020; Xu et al., 2020), we hypothesize that CoV activate AhR, but the IDO1-kynurenine-AhR pathway may be inactive (Fig. 1). If so, the fate of viral infection may depend on the state of background AhR activation, which is determined by environmental pollutants, gender, age, diet, physical activity, and comorbidities. We hypothesize that as long as AhR remains activated due to CoV infection and the symptoms are mild, eliminating factors known to up-regulate AhR, or implementing means known to down-regulate AhR should decrease severity of infection. When infection by CoV has been fully established, and physicians care for patients suffering from severe symptoms (Huang et al., 2020; Oxley et al., 2020; Xu et al., 2020), we hypothesize that the IDO1-kynurenine-AhR pathway is continuously activated due to protracted inflammation in addition to CoV mediated activation of AhR. Such a vicious circle can only be efficiently interrupted by simultaneous down-regulation of both AhR and IDO1 (Fig. 1). A medication addressing activity of both AhR and IDO1 simultaneously is dexamethasone (Ott et al., 2015; Vrzal et al., 2009), a glucocorticoid with a broad range of uses including asthma, chronic obstructive pulmonary disease, and rheumatoid arthritis.

10. AhR alone

AhR was discovered as a receptor binding and mediating toxicity of the environmental dioxin TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) (Okey, 2007; Opitz et al., 2011). This initial observation may indicate that humans frequently exposed to environmental and other toxins activating AhR such as dioxins or pesticides may be more prone to, and at

risk of, contracting infection due to CoV more easily. Surprisingly, calcitriol (vitamin D_3) in addition to its main mechanisms of action, may down-regulate expression of the AhR gene (Takami, Fujimaki, Nishimura, & Iwashima, 2015). More surprisingly, deficiency of vitamin D_3 has indeed been reported to contribute to acute respiratory distress syndrome with fatalities increasing with age and comorbidities, both being associated with lower concentrations of vitamin D (Grant et al., 2020). The concentration of vitamin D decreases with age leaving the elderly particularly prone to viral infections including SARS-CoV-2, which is reflected in the pattern of Covid-19 during the current pandemic. If confirmed in epidemiological studies, supplementation of vitamin D during winter should be recommended to all, and particularly in the elderly since vitamin D may down-regulate the AhR gene (Takami, Fujimaki, Nishimura, & Iwashima, 2015), therefore decreasing susceptibility to viral infections.

11. IDO1 alone

IDO1 is a cytosolic, rate-limiting enzyme in the conversion of tryptophan, via kynurenine, which is a ligand of and activates AhR (Jaronen, & Quintana, 2014), towards synthesis of nicotinamide (Mellor, Lemos, & Huang, 2017). Activation of IDO1 depresses T lymphocytes activation by starving them of tryptophan through its conversion to kynurenine (Neavin, Liu, Ray, & Weinshilboum, 2018). IDO1 gene transcription can be up-regulated by multiple viral, microbial and parasitic pathogens, cancers, or pregnancy (Benavente et al., 2019; Larigot, Juricek, Dairou, & Coumoul, 2018; Neavin, Liu, Ray, & Weinshilboum, 2018) or it can be induced by the pro-inflammatory cytokine INF-γ (Neavin, Liu, Ray, & Weinshilboum, 2018) limiting host immune response by means of generation of FOXP3(forkhead box P3)-expressing regulatory T cells to inhibit other cells of the immune system (Larigot, Juricek, Dairou, & Coumoul, 2018; Neavin, Liu, Ray, & Weinshilboum, 2018).

The most popular drug down-regulating IDO1 is tocopherol/vitamin E (Stapelberg et al., 2013). Vitamin E is an antioxidant that scavenges radicals, terminates oxidation of polyunsaturated fatty acids, and has multiple immunomodulatory actions such as on lymphocyte proliferation, prostaglandin E2 synthesis, affects gene transcription and translation, and it influences cell membrane and signal transduction

(Lee, & Han, 2018). It is intriguing that up to 60% of adults in the United States have too low vitamin E intake (<12 mg/d) (Fulgoni, Keast, Bailey, & Dwyer, 2011). Drawbacks of such a low intake are dysregulation of immune and inflammatory responses and decreased resistance to infections with elderly humans being hit the most. This is due to the fact that aging pathogen defense-related immune responses are weaker and inflammatory responses prolonged (Meydani, Lewis, & Wu, 2018). It is therefore conceivable, that insufficient supply with vitamin E may contribute to increased susceptibility in the elderly to infection with CoV and may promote severity of Covid-19. Supplementation of vitamin E in elderly could reduce the risk of, and morbidity from, infections with CoV. This has intuitively been recognized in Great Britain where Covid-19 patients were supplemented with vitamins (Calder, Carr, Gombart, & Eggersdorfer, 2020).

12. Habits may modulate AhR

In healthy conditions, tryptophan is metabolized to kynurenine by tryptophan-2,3-dioxygenase (TDO) in the liver and by IDO1 in the brain and peripheral tissues such as small intestine, lungs, female genital tract or placenta (Badawy, 2017; Castro-Portuguez, & Sutphin, 2020; Sedlmayr, 2007). In addition, significant amount of kynurenine is metabolized by exercising muscles (Agudelo et al., 2019; Martin, Azzolini, & Lira Ruas, 2020) and a small amount is used to activate AhR in response to minor inflammatory processes (Badawy, 2017). Disrupting this healthy balance by immobility such as through stay-at-home orders, may lead to an increase in kynurenine and its availability to activate AhR, therefore increasing an individual's risk to become prone to infection (Agudelo, 2019; Martin, Azzolini, & Lira Ruas, 2020). Therefore, physical exercise during quarantine should be encouraged.

In advanced disease, if liver function decreases and ceases (Zhang, Shi, & Wang, 2020) and muscles are not stimulated due to immobilization in the hospital, AhR may become overwhelmed with kynurenines and activated via the IDO1-kynurenine-AhR pathway. If such patients are subjected to intensive therapy in the ICUs, principles of care established to excel under regular conditions should perhaps be expanded by following biomarkers of tryptophan metabolism related to inflammation (Badawy, & Guillemin, 2019).

13. Lessons to learn

Persistent activation of AhRs by CoV may lead to up-regulation of multiple sets of downstream effectors governed by AhRs resulting in different phenotypic disease pictures depending on time after infection, individuals overall state of health, comorbidities, and environmental and other factors modulating AhRs.

CoV are perfect viruses invading hosts by avoiding collision with other pathogens because of activating the AhR when bypassing the IDO1-kynurenine-AhR pathway. This pathway is employed by multiple, viral, microbial and parasitic pathogens to establish infection. This peculiarity enables massive up-regulation of multiple AhR-dependent downstream effectors, whereas self-restricting mechanisms may remain at bay.

Therapies selectively down-regulating both AhR and IDO1 are currently lacking and should be considered in the future by public and private innovation driven research organizations as therapies for viral infections. However, such therapies should be designed to leave physiological functions of both AhRs and IDO1 intact. Since dexamethasone may down-regulate both AhR and IDO1 genes, in addition to its main mechanism of action, and is known to play a role in inflammatory diseases, its use in therapy of Covid-19 should be studied in rigorous interventional trials.

Since calcitriol may down-regulate the AhR gene and is known to play a role in the spread of other viral infections, supplementation of calcitriol should be reviewed in epidemiological studies and tested in prospective trials for prevention of SARS-CoV-2 infections.

Supplementation of tocopherol should be reviewed in epidemiological studies and tested in prospective trials for prevention of SARS-CoV-2 infections in elderly since tocopherol may down-regulate IDO1 gene and is known to play a role in response to viral infections and inflammation in aging.

Associations and conclusions revealed by our analyses should be considered with particular caution because we are reporting changes in the expression of genes only. Such changes need to be translated into biological actions by multiple associated mechanisms, which have not been evaluated in our analyses. Therefore, our hypotheses offer no information or confirmation of clinical therapeutic value of any discussed therapy in modulating of SARS-CoV-2 infection. Before any conclusion can be drawn

regarding a potential benefit of our recommendations regarding any medication in patients with Covid-19 randomized controlled clinical trials and large observational population studies evaluating our concepts will be necessary.

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Note

Data mining on the AhR and IDO1 genes

We conducted a gene expression data mining aimed to identify conditions under which AhR and IDO1 undergo simultaneous upregulation. When the search was limited to human lung-derived samples, we confirmed that increased expression of AhR and IDO1 genes occurred in response to viral infections, including SARS-CoV-2 and respiratory syncytial virus (RSV) (Fig. 3A). This was accompanied by elevation of proinflammatory gene expression, activation of the TF/PAI-1 signaling pathway, and upregulation of CYP1A1 (Fig. 3A).

In parallel, we investigated drugs in clinical use for propensity of affecting the expression of both AhR and IDO1 genes by means of integrative analysis of bioinformatics data collected on human and non-human tissues to discover how the suspected key drivers of infection mediated by CoV and perhaps by SARS-CoV-2, AhR and IDO1, can be affected by medications already employed to treat other human diseases.

Surprisingly, there are licensed drugs possessing such dual antagonistic properties (Fig. 3B) such as rosiglitazone (antidiabetic), dexamethasone and betamethasone (glucocorticoids with broad range uses including asthma, chronic obstructive pulmonary disease and rheumatoid arthritis), infliximab (TNF-α inhibitor), isoniazid (antituberculotic), niacinamide (vitamin B_3, dietary supplement), levonorgestrel (progestogen), promazine (neuroleptic), curcumin (herbal dietary supplement), lidocaine (local anesthetic and antiarrhythmic), and amitriptyline (antidepressant and anxiolytic). Calcitriol (vitamin D_3) and fluticasone (steroid used for therapy of asthma and chronic obstructive pulmonary disease), preferentially down-regulated the AhR gene in the context of this analysis (Fig. 3B).

No clinical data supporting use of any medications listed in Fig. 3B in therapy or prevention of CoV infections currently exist, nor is it known if any, how, and in which phase of the disease these medications can be recommended for use. Rigorous clinical trials are necessary before any recommendation regarding future use of these medications in therapy of CoV infections, including Covid-19, can be made.

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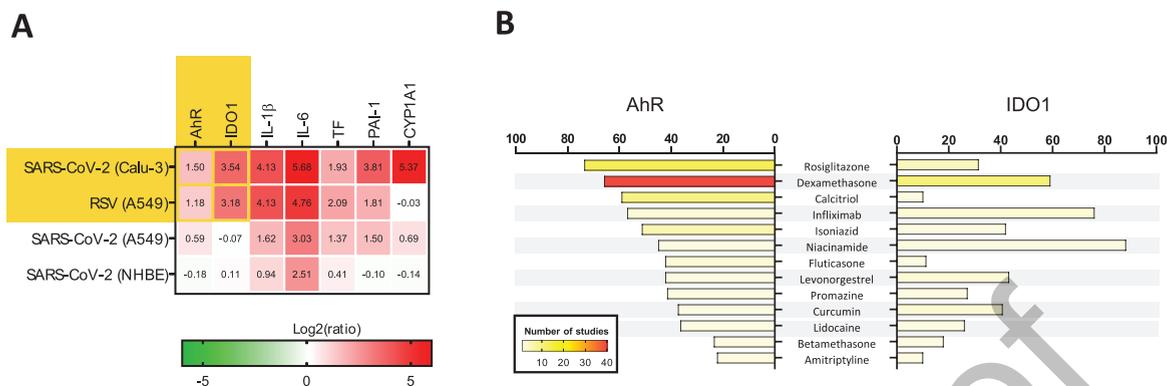
Fig. 3. Data mining on the modulation of AhR and IDO1 genes. (A) Conditions under which both AhR and IDO1 genes undergo upregulation were identified using biclustering tool of Genevestigator 7.6.0 (www.genevestigator.com) (Hruz et al., 2008). Query was limited to mRNAseq data from human lung tissues and cell lines. The results are marked with yellow background. It was revealed that significant up-regulation of *AHR* and *IDO1* occurred in the lung adenocarcinoma cell line Calu-3 samples infected with SARS-CoV-2 (USA-WA1/2020 isolate) at a MOI (multiplicity of infection) of 2 and harvested 24 h post-infection (hpi) versus mock-infected Calu-3 cells. Similar observation was made in human lung adenocarcinoma cell line A549 samples infected with respiratory syncytial virus (RSV) A2 strain (MOI 2; 24 hpi) in comparison to mock control (Blanco-Melo et al., 2020). There were no other experimental results demonstrating concurrent upregulation of *AHR* and *IDO1* in the human lung in the Genevestigator database encompassing 2536 mRNAseq studies. Initial heatmap (yellow background) was extended with data on the expression profile of genes driving the AhR-dependent pathologies: inflammation, thrombosis, and fibrosis (Fig. 2). The specific genes code for (1) proinflammatory interleukin 1β (IL–1β) and interleukin 6 (IL-6); (2) thromboembolism-related tissue factor (TF) and plasminogen activator inhibitor-1 (PAI-1); and (3) fibrosis-related P450 cytochrome 1A1 (CYP1A1). Data from A549 and Normal Human Bronchial Epithelial (NHBE) cells infected with SARS-CoV-2 (MOI 2, 24 hpi) were provided for reference. (B) Medications modulating the expression of AhR and IDO1 genes were identified using Pharmaco Atlas of the BaseSpace Correlation Engine software suite (www.nextbio.com) (Kupershmidt et al., 2010). A p-value significance cutoff of 0.05 (without any multiple testing correction) and a minimum absolute fold-change cutoff of 1.2 were used by the software for identification of medications affecting expression of the genes of interest. Then, grading of significant factors was conducted based on the following conditions: (1) total number of medication specific studies in which the gene was measured; (2) number of medication-specific studies in which the gene's expression was found to be significantly altered; (3) gene's degree of down- or up-regulation in comparison to all other genes with altered expression within each of the medication studies; (4) consistency of the gene's association across the medication studies. Additional statistical criteria were applied, such as correction for multiple hypothesis testing, to finally rank the medications. The most significant result was assigned with a numerical score of 100, and the other medications' scores were normalized to the top-ranked result. Analyses were performed separately for AhR and IDO1 genes. Only medications significantly downregulating both genes were plotted. Numbers of studies are shown by means of the color scale ranging from light yellow ($n = 1$) to dark red ($n = 40$).