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Psychosocial Risk Factors, Noncommunicable Diseases, and Animal Models for COVID-19

To the Editor:

As summarized by several recent papers, numerous species can be infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), thus representing useful models for coronavirus disease 2019 (COVID-19) (1). While hamsters, ferrets, monkeys, and other species can be infected by SARS-CoV-2, mice cannot, emphasizing the utility of recently developed humanized mouse models, and viral vectors expressing human angiotensin-converting enzyme 2 (hACE2), the main target of SARS-CoV-2 (1,2). However, there are considerable limits if such approaches predominately utilize healthy young experimental subjects (1) or if viral infection is lethal in a high proportion of mice within a few days (2), a condition that is not observed in humans.

Nearly All Subjects With Severe Cases of COVID-19 Have Multiple Preexisting Noncommunicable Diseases

With most COVID-19 cases being asymptomatic, with no robust evidence that disease severity associates with genetic predisposition (3,4), and with aging being a well-documented risk factor, it is significant that 90% of individuals with severe cases requiring hospitalization have multiple preexisting noncommunicable diseases (NCDs). Common NCDs in COVID-19 patients are type 2 diabetes, hypertension, obesity, and chronic lung disease (Table 1).

Psychosocial Stress Increases Risk for Disease Susceptibility

Critically, several studies confirmed that severity of COVID-19 is disproportionately common in patients from low socioeconomic status (SES) groups and minorities experiencing multimorbidity and low life expectancy (5,6). The high susceptibility conferred by low SES can be explained in part by living in high-density housing, not having the option to comfortably quarantine, having unsafe working conditions, living with poor ventilation and air quality, and so forth. However, it has long been recognized that a gradient in the impact of SES on health exists in virtually any context in which this has been assessed, including in wealthier societies (5). Low SES strata are characterized by unpredictable and uncontrollable living conditions, high-stress biomarkers, and cumulative negative life events (7–9), and it is increasingly accepted that the risk conferred by low SES can be at least in part attributed to an underlying biology that is only recently starting to emerge and to be investigated at the physiological and molecular levels (5,8,10,11). Another indirect evidence that chronic stress can be involved in COVID-19 pathogenesis comes from the beneficial effect of dexamethasone for severe cases (12). Dexamethasone, in addition to limiting inflammation via glucocorticoid receptor-mediated activation, is well known to

suppress the endogenous stress-related hypothalamic-pituitary-adrenocortical axis (13) and thus the endogenous secretion of adrenocorticotrophic hormone and cortisol, two of the major stress hormones (14). Thus, it is reasonable to speculate that the inhibition of the endocrine stress response is among the benefits of short-term dexamethasone treatment in patients affected by COVID-19.

Overall, diseases exacerbating the COVID-19 prognosis appear to be highly sensitive to psychosocial risk factors. In particular, psychosocial stress mediates much of the link between low SES and high prevalence of NCDs (7,8); commensurate with that, NCDs and life-threatening COVID-19 outcomes disproportionately impact low SES communities and disadvantaged minorities (5,15).

Chronic Social Stress Animal Models Recapitulate the Multiple Comorbidities Increasing Risk for Severe COVID-19

These risk factors suggest that the conventional approach of cross-breeding humanized models of COVID-19 with monogenetic models of human disease, using pharmacological or surgical models (Table 1), or injecting viruses in mice expressing hACE2 in the same disease models, should not be the preferred approach, as it is unlikely to model the complexity of human risk factors. Consistent with this idea, SARS-CoV-2 injection in even healthy young mice engineered to express hACE2 rapidly resulted in death (2). Such risk factors suggest the importance of alternative approaches and the need to combine humanized mouse models of COVID-19 with models of multiple comorbid NCDs.

Here, we provide a rationale for the use of social and behavioral laboratory models of multiple comorbidities, including obesity, hypertension, cardiovascular disease, and accelerated senescence, in the study of COVID-19. Extensive research, including our own, has focused on models of chronic social stress that are contingent on negative social relationships built around uncontrollable and perceived potential life-threatening conditions (9,16,17). Such stress-based models can be ideal for studying the interactions between COVID-19 and NCDs. These are arguably the most potent and reliable (nongenetic and nonpharmacological) models to induce multiple comorbid disease observed in severe cases of COVID-19, such as obesity, type 2 diabetes, hypertension, a proinflammatory state, neurological and neuropsychiatric diseases, and accelerated aging, overall resulting in a shortened lifespan (18) (Table 1). Thus, we advocate for a research focus on 1) studies of humanized COVID-19 mice undergoing classic psychosocial stress models for worsening NCDs relevant to COVID-19 risk and 2) the use of hACE2 viral vectors coupled with such psychosocial stress models in wild-type animals, particularly old subjects. An interesting new opportunity provided by the selection of mutant SARS-CoV-2 viruses capable of infecting common laboratory strains of mice (19) is to pair the use of these viruses with chronic psychosocial stress paradigms in order to optimally model the human condition.

Table 1. List of Preconditions Increasing Severe COVID-19 and Animal Models of Diseases

CDC List of Medical Conditions That Increase a Person's Risk of Severe Illness From COVID-19 ^a			Laboratory Rodent Models for These Medical Conditions	
Level of Evidence	Condition	Evidence of Impact on COVID-19 Severity	Conventional Genetic, Pharmacological, or Surgical Models ^b	Disease Manifested by Laboratory Rodents Exposed to Chronic Social Stress
Strongest and Most Consistent Evidence	Cancer	Systematic review (21) Cohort study (22,23) Case series (24)	Cell line–derived xenograft; genetically engineered mouse cancer model (25,26)	Exacerbates the disease in genetic or xenograft inoculation models; spontaneous tumor development during aging (18,27)
	Chronic kidney disease	Case series (28–30) Cohort study (31–33)	Cisplatin injection; subtotal nephrectomy, DOCA-salt (34,35)	Exacerbates the disease in genetic models or vulnerable strains (27,36)
	COPD	Meta-analysis (37,38) Cohort study (32)	Elastase; chronic cigarette smoke exposure (39)	NA
	Heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies	Cohort study (40,41) Meta-analysis (37,42) Case series (43)	Surgical pressure overload; ischemia-reperfusion injury; metabolic syndrome models (44)	Sustained tachycardia, arrhythmia; cardiac hypertrophy in some model; exacerbates cardiac disease in genetic models (45,46)
	Obesity (BMI ≥30 kg/m ²)	Cohort study (29,47–51) Cross-sectional study (52)	ob/ob; db/db; diet-induced obesity (53,54)	Causes hyperphagia and weight gain/obesity (model specific) (17)
	Severe obesity (BMI ≥40 kg/m ²)	Cohort study (55) Cross-sectional study (56) Meta-analysis (57)	ob/ob; db/db; diet-induced obesity (53,54)	No morbid obesity has been reported
Mixed Evidence	Type 2 diabetes mellitus	Case series (29) Longitudinal study (58) Cohort study (59,60) Meta-analysis (61) Cross-sectional study (62)	B6 ob/ob; BKS db/db; Zucker diabetic fatty; TALLYHO/JngJ (63)	Causes pre–type 2 diabetes and metabolic syndrome in WT; exacerbates diabetes in genetic strains (17,64)
	Asthma	Cohort study (32,64–68) Case series (68)	BALB/c injected with ovalbumin house dust mite (69)	Enhances allergen-induced airway inflammation (70)
	Cerebrovascular disease	Meta-analysis (71–74) Synthesis of evidence (75) Cohort study (40,41,76–78)	Intracarotid injection of occlusive microbeads/cholesterol crystals; carotid artery stenosis; BCAS mice (79,80)	Exacerbates stroke outcome and cerebrovascular disfunctions (81,82)
	Hypertension	Cohort study (32,40,41,83–85) Case series (86) Systematic review (87) Meta-analysis (37,42,88,89)	SHR rats; BPH mice; DOCA-salt; AngII injection (35)	Causes persistent increase in mean arterial pressure and heart rate (46,90)

AngII, angiotensin II; BCAS, bilateral common carotid artery stenosis; BMI, body mass index; CDC, Centers for Disease Control and Prevention; COPD, chronic obstructive pulmonary disease; db/db, diabetic mice; DOCA, deoxycorticosterone acetate; NA, not available; ob/ob, obese mice; SHR, spontaneously hypertensive rat; WT, wild-type.

^aFrom (91).

^bOnly the most common models are described in this table: “strongest and most consistent evidence” = consistent evidence from multiple small studies or a strong association from a large study (CDC classification); “mixed evidence” = multiple studies that reached different conclusions about risk associated with a condition (CDC classification). The “limited evidence” category from the CDC website was omitted from this table. Additional references and preprints are available (91).

Conclusions

Mental stress has been advocated as a consequence of the COVID-19 pandemic, leading to negative long-term risk for psychopathologies (20). Here, we suggest that the reverse should also be considered. A direct causal effect of chronic stress mediators and underlying multiple comorbidities should be considered as a leading risk factor for this new disease. The catastrophic impact of SARS-CoV-2 is deeply intertwined with NCDs and psychosocial risk factors, and the use of naturalistic NCD models more closely reflecting the human disease seems essential.

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