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Commentary

Variation in Thyroid Hormone Metabolism May Affect COVID-19 Outcome

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Abbreviations: ACE, angiotensin-converting enzyme; T3, 3,5,3′-triiodothyronine.

The study by de Lima Beltrão and colleagues (1) indicates a protective role by the heterozygous state of the *DIO2* polymorphic variant (Thr92Ala; rs225014) on the outcome of COVID-19 disease. Heterozygous patients would be protected 47% by intrahospital mortality. Logistic regression analysis confirmed the association of the Thr/Ala genotype with reduced mortality when compared to Thr/Thr, even after correcting for 14 comorbidities and other covariates. The protective role of the Thr92Ala heterozygosity was then confirmed in a meta-analysis including 21 studies on thousands of cases with variable disease conditions and controls. In 5 of these studies, the heterozygous *DIO2* genotype would provide significant protection against disease severity.

Though lacking a conclusive explanation for their findings, the authors suggest the protective role played by the Thr92Ala-DIO2 heterozygosity may be due to overdominance, that is, a heterozygous advantage in which heterozygous individuals have better fitness than homozygous individuals. Overdominance is a well-known selection mechanism by which an allele is actively maintained in the population longer than expected from genetic drift alone (2). By this mechanism, host-pathogen interactions have shaped genetic variants in populations (3). Indeed, *HBB* variants responsible for sickle anemia and thalassemia confer protection against malaria, variants in the *CFTR* gene responsible for cystic fibrosis protect against cholera toxin, variants of *HEXA* involved in Tay-Sachs disease are associated with resistance to tuberculosis, while single-nucleotide variations in human *NPC1* (the gene involved in Niemann-Pick disease type C1) influence the entry into cells of filoviruses, like Ebola and Marburg. Thus, the possible protective effect of the *DIO2* genotype against COVID-19 and other diseases is also intriguing in light of other data suggesting a role for *DIO2* genotype in human evolution (4).

The DIO2 variant rs225014 causes the nonconservative missense replacement of a threonine residue with an alanine at the codon 92 of in exon 2 of the *DIO2* gene (Ala92-D2). This change has a high frequency in the general population as the frequency of the T/T (Thr/Thr), C/T (Ala/Thr), C/C (Ala/Ala) genotype is found in 30%, 48% and 22% of samples (see the 1000 Genomes Project).

The effect of this variant on the catalytic function of D2 is debated as in vitro studies on HEK-293 and COS cells failed to demonstrate a reduced activity, but the Ala92-D2 variant was less efficient than Thr92-D2 in converting thyroxine into 3,5,3′-triiodothyronine (T3) in an in vivo model of myoblast and pituitary cells from Dio2-null mice (5), indicating the Ala92-D2 is associated with reduced production of bioactive T3 at local sites. Moreover, the residue 92 is located within a 6 amino-acid stretch involved in D2 clearance by ubiquitination and electron microscopy studies have identified the ectopic localization of the Ala92-D2 in the Golgi along with altered expression of Golgi markers and endoplasmic reticulum stress (6).

The whole of these data suggest tissue availability of T3 might play a role in the outcome of COVID-19 and other several other organ-specific conditions. A recent cross-sectional study (7) found an association between hypothyroidism and reduced SARS-CoV-2 infectivity in a large public data set (UC CORDS). A total of 11 375 hypothyroid patients were tested for COVID-19, with a statistically significantly lower infection rate compared to those without hypothyroidism in male and female participants. One possible explanation relies on the crosstalk between thyroid hormones and the renin-angiotensin system. Angiotensin-converting enzyme type 2 (ACE2) is a key molecule for SARS-CoV-2 infection mediating the virus entry into the cells, and its activity was shown to be influenced by thyroid dysfunction both at the circulating and tissue levels (8). In experimental hypothyroidism, the cardiac ACE2 expression was found to be reduced. Similarly, reduced serum and liver ACE concentrations were reported in neonatal and adult rats with hypothyroidism, whereas hyperthyroid rats and patients showed an increase in serum ACE concentrations directly correlated with thyroid hormone levels. Pulmonary ACE activity in rats is low at

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birth and increases with age; this increase is larger in euthyroid rats than in congenitally hypothyroid animals (8). Nevertheless, the Ala92-D2 homozygosity was not as protective as the Thr92Ala heterozygous state in this study, thus indicating other effects beyond the D2 enzymatic activity and the tissue T3 availability. The authors allude to a possible effect of Thr92Ala variation on endoplasmic reticulum stress, and the latter would play a relevant role in the inflammatory response and lung inflammatory diseases. In previous studies, the authors documented the association of the heterozygous Ala/Thr-D2 genotype with inflammatory markers, such as CXCR4 and SLC44A that are today known to also play a relevant role in the most severe manifestations of COVID-19 disease (1, 6).

The limited sample of COVID-19 patients and the exclusive enrollment of intensive care unit patients with severe manifestations are the main weaknesses of this study (1). But the whole of these findings and considerations, including the broad effect on the outcome of several disease conditions, indicates the need for a) additional *DIO2* genotyping studies on larger cohorts of patients with variable clinical manifestations to confirm the protective role of this *DIO2* genotype (and the consequent variation in thyroid hormone metabolism) on COVID-19 outcome; and b) experimental approaches to understand the biological mechanism underlying the plausible protective role of the DIO2 heterozygosity against severe disease outcomes.

Disclosures

The authors have nothing to disclose.

Data Availability

Data sharing is not applicable to this article because no data sets were generated or analyzed during the present study.

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