SARS-CoV-2 severity in African Americans – a role for Duffy null?

The scourge of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; COVID-19) infection in the United State has disproportionately affected African Americans, Hispanics, and Native Americans;[1] a study in the United Kingdom found Blacks and Asians to have augmented risk.[2] We here focus upon African Americans (AA), a subpopulation in which COVID-19 disease is more likely to occur and to result in disproportionately higher hospitalization and mortality rates. The latter is typically from pneumonitis progressing to a severe acute lung injury (ALI) syndrome.

Identifying specific reasons for this disparity is challenging because severity is influenced by comorbidities as well as societal and environmental factors. Not surpri-singly, for the pandemic in general, emerging data are beginning to suggest contributory biological variabilities that reside within the genetic background.[3] Here we suggest that a predisposition to severe COVID-19 pneumonitis amongst infected AA is established by an erythroid Duffy blood group polymorphism.

Duffy blood group antigens, membrane proteins FYa and FYb, are allelic products of *DARC* (Duffy antigen chemokine receptor), now known as *ACKR1* (atypical chemokine receptor 1).[4] FY proteins are expressed on red blood cells (RBC) and endothelial cells of capillaries and venules (as well as on cerebellar neurons and epithelial cells of the kidney and lung). Normally, erythroid FY binds multiple inflammatory chemokines, probably functioning as a chemokine reservoir that helps regulate plasma levels.[5] RBC FY can dampen leukocyte activation, and endothelial FY guides localization and presentation of chemokines. Specifically, endothelial FY located at sites of endothelial cell/cell contact regulates chemokine transcytosis and leukocyte diapedesis.[4,6]

Relevance to COVID-19 amongst AA derives from a *DARC* polymorphism (rs2814778, a T→C substitution in the promoter's GATA box) that prevents erythroid expression of both FY proteins, while FY expression on endothelial cells is unaffected.[4] Homozygosity results in the "Duffy null" phenotype. Because Duffy null protects from RBC invasion by *Plasmodium vivax*, its positive selection led to its current >95% prevalence in Western and South-Western sub-Saharan Africa.[7] Its prevalence is somewhat lower, although still very high, in the remainder of sub-Saharan Africa. Consequently, perhaps 67% of African Americans are erythroid Duffy null.

Under normal circumstances Duffy null accounts for benign ethnic neutropenia amongst AA, but it also exerts a pro-inflammatory effect that can promote leukocyte migration into the lung.[4] This is the basic reason to suspect that erythroid Duffy null status would promote COVID-19 pneumonitis and accentuate its severity, resulting in ALI. In support, a 2012 analysis of three prior human studies revealed that, if inflammatory ALI deve-lops for some reason in Duffy null AA, it is significantly more severe than in either Duffy positive AA or European Americans. Specifically, erythroid Duffy null patients had a 17% higher risk of mortality, as well as fewer ventilator-free and organ failure-free days.[8]

We emphasize that there are likely multiple variables contributing to COVID-19 disease. Susceptibility (infectivity) and severity may have separate determinants, and various human subpopulations are likely to have their own unique risk factors. The role of genetics in influencing a great variety of infectious diseases is well known. For example, HIV (human immunodeficiency virus) attaches to Duffy protein on RBC which then present HIV to target cells.[9] It is reported that in Duffy null individuals, HIV infectivity is substantially higher. We find no analogous studies addressing the infectivity issue for SARS-CoV-2. We do note, however, that the Duffy proteins carry sialic acid, and multiple other coronaviruses have been described as binding to sialic acid-exposing proteins.[10] Interestingly, interaction with Duffy sialic acids is the mechanism by which *Plasmodium vivax* begins to infect Duffy positive RBC.

It will be interesting, when data become available, to see if COVID-19 is particularly severe in AA with sickle cell anemia (SCA). On the face of it, one might well expect so. However, SCA individuals already have a (subclinical) cytokine storm and activated leukocytes at baseline; they are, therefore, very likely at baseline to have abnormal activation of the vast number of leukocytes sequestered within the pulmonary microvasculature. Since they thus seem to be on the precipice of catastrophic pulmonary inflammation even at baseline, it seems entirely possible that in SCA COVID-19 is so very severe that any influence of Duffy status is simply overwhelmed by the SCA biology itself. A single study has looked at COVID-19 in SCA, but it registered only the presence/absence of specific disease features i.e., not their severity.

In summary, we suggest that the greater severity of COVID-19 in African Americans reflects, at least in part, the biological impact of an underlying Duffy null state. Duffy status can easily be documented and, we speculate, this might aide in risk stratification at COVID-19 disease onset.

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