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Review

Protection against COVID-19 in African population: Immunology, genetics, and malaria clues for therapeutic targets

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ABSTRACT

Background: There is a marked discrepancy between SARS-CoV-2 seroprevalence and COVID-19 cases and deaths in Africa.
Main: SARS-CoV-2 stimulates humoral and cellular immunity systems, as well as mitogen-activated protein kinase (MAPK) and nuclear NF-kB signalling pathways, which regulate inflammatory gene expression and immune cell differentiation. The result is pro-inflammatory cytokines release, hyperinflammatory condition, and cytokine storm, which provoke severe lung alterations that can lead to multi-organ failure in COVID-19. Multiple genetic and immunologic factors may contribute to the severity of COVID-19 in African individuals when compared to the rest of the global population. In this article, the role of malaria, NF-kB and MAPK pathways, caspase-12 expression, high level of LAIR-1-containing antibodies, and differential glycophorins (GYPA/B) expression in COVID-19 are discussed.
Conclusion: Understanding pathophysiological mechanisms can help identify target points for drugs and vaccines development against COVID-19. To our knowledge, this is the first study that explores this link and proposes a biological and molecular answer to the epidemiologic discrepancy in COVID-19 in Africa.

1. Background

The novel coronavirus disease (COVID-19) is caused by severe acute respiratory syndrome (SARS) coronavirus 2 (SARS-CoV-2), which rapidly spread globally (Wang et al., 2020). As of 21 August 2020, there have been 22,536,278 confirmed cases of COVID-19, including 789,197 deaths, reported to WHO (Rokni et al., 2020). The disease has a mortality rate of 3.5 % although this widely varies across different countries. African mortality from COVID-19 is 1.7 %, almost half of the global mortality (3.3 %) and three-fold lower than European mortality (5.7 %). Uyoga et al. recently reported the seroprevalence of anti-SARS-CoV-2 IgG antibodies in Kenyan blood donors. This study was the first national and regional estimation of population exposure to SARS-CoV-2 in an African country. Results showed that three urban counties, namely Mombasa, Nairobi, and Kisumu, had the highest prevalence, with 9.3 %, 8.5 %, and 6.5 % respectively, which sharply contrast with the minimal number of COVID-19 cases and deaths reported during the same period. The crude prevalence was 5.6 %, while the population-weighted, test-adjusted seroprevalence was 5.2 %. The cause of this discrepancy is currently unknown (Uyoga et al., 2020).

Various investigations have discussed the vulnerability of African populations to the expansion and higher incidence of COVID-19 since the continent has experienced endemic diseases, such as tuberculosis, human immunodeficiency virus, and malaria in recent decades, in addition to emerging and re-emerging infectious pathogens, such as Lassa haemorrhagic fever or Ebola virus disease (Nkengasong and Mankoula, 2020). One factor that facilitates the rapid spread of diseases in Africa is population density (Velavan and Meyer, 2020). Gilbert et al. (2020) argued that this risk is unequal and depends on the number of air connections with China, especially with Guangdong—the origin of the pandemic (Shereen et al., 2020). In this case, Egypt, Algeria, and South Africa were more exposed compared with Nigeria, Ethiopia, Sudan, Angola, Tanzania, Ghana, and Kenya that had moderate risk (Gilbert et al., 2020). This situation caused the WHO's concern for and anticipation of rapid expansion. Nevertheless, the WHO Director General on 25 May stated, "Africa's knowledge and experience of suppressing infectious diseases have been critical to rapidly scaling up an agile response to COVID-19" (WHO, 2020). This fact is supported by the number of infected and deceased in Africa, which is much lower than expected. Researchers have tried to explain the psychosocial aspect of

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confinement, saying that the African population has high levels of awareness about the dangers of these pandemics (El-Sadr and Justman, 2020) since they have suffered from epidemics in recent years (Nkengasong and Mankoula, 2020). This, in turn, improved the containment procedures of African health systems, an aspect that cannot fully explain lower mortality in the country; hence, this work analyses possible molecular determinants.

2. Main

Previous coronaviruses (i.e. SARS-CoV and MERS-CoV) were characterized by fast and robust initial virus replication with late IFN generation, resulting in disproportionate inflammatory host response (Allegra et al., 2020). SARS-CoV-2 uses angiotensin-converting enzyme II (ACE2) and a transmembrane serine protease (TMPRSS) as cell entry receptors, followed by a cytokine-related syndrome and acute respiratory distress syndrome (ARDS), which is induced by the hyperactivation of the nuclear factor kappa B (NF-kB) most likely in nonimmune cells, including lung epithelial cells (Hirano and Murakami, 2020). Then, SARS-CoV-2 stimulates humoral and cellular immunity systems as well as mitogen-activated protein kinase (MAPK) and nuclear NF-kB signalling pathways, which regulate inflammatory gene expression and immune cell differentiation (Wu and Yang, 2020). The result is pro-inflammatory cytokines release (Li et al., 2020), hyper-inflammatory condition, and cytokine storm that provoke severe lung alterations (Kindler and Thiel, 2016; Channappanavar et al., 2016) and may result in multi-organ failure in COVID-19 (Jafarzadeh et al., 2020).

The Janus kinase signal transducer and activator of transcription JAK/STAT pathway is the principal signalling mechanism for a wide array of cytokines and growth factors. All cytokines need JAK signalling to exert their functions (Dennis, 2003). JAK activation stimulates cell proliferation, differentiation, migration, and apoptosis (Rawlings et al., 2004). JAK/STAT-mediated NF-kB activation by coronaviruses (i.e. SAS-CoV or MERS) is responsible for mediating the production of pro-inflammatory cytokines and chemokines. Therefore, NF-kB plays a key role in the pathogenesis of coronaviruses (DeDiego et al., 2014; Kanzawa et al., 2006; Yang et al., 2017). It has been observed that tyrosine kinase activity is increased in COVID-19 (McGee et al., 2020), which leads to phospholipase C (PLC) activation that actives protein kinase C (PKC). This induces reactive oxygen species (ROS) increase, ROS-mediated NF-kappa B (NF-kB) activation, and mTOR inhibition, which result in the transcriptional activation of NF-kB target genes. These genes include anti-apoptotic and survival factors, positive cell-cycle regulators, and pro-inflammatory genes, leading to cytokine production, which in turn increases autophagy (Volpe et al., 2018; Jost and Ruland, 2007) and facilitates viral replication and cytokine storm.

A study of host responsive genes (HRG) for SARS-CoV-2 showed that they are especially enriched in IL-17 signalling, cytokine-cytokine receptor interaction, and NF-kB pathways, among other proceses (Qin et al., 2020). Research has indicated that the NF-kB pathway, which is induced by several mediators, plays a role in cytokine storm (Mozafari et al., 2020). IL-6 also has a pivotal role in cytokine storm because it activates the JAK/STAT signalling pathway (Luo et al., 2020; Kang et al., 2019; Garbers et al., 2018). Elevated serum levels of IL-6 are commonly reported in patients with severe COVID-19 and correlate significantly with nonsurvivors (Ruan et al., 2020; Giamarellos-Bourboulis et al., 2020). Overall, NK-kB, JAK/STAT, and MAPK pathways are critical in COVID-19 pathogenesis.

In the following sections, the role of malaria, NF-kB, and MAPK pathways, expression of caspase-12, higher levels of LAIR-1-containing antibodies, and differential glycophorins (GYPA/B) expression in COVID-19 are discussed.

3. Malaria

The malaria parasite *Plasmodium falciparum* kills on the order of a million African children each year (Snow et al., 2005), and this is a small fraction of the number of infected individuals in the population (Snow et al., 2005; Greenwood et al., 1987; Mackinnon et al., 2005). In communities where everyone is repeatedly infected with *Plasmodium falciparum*, host genetic factors account for around 25 % of the risk of severe malaria, which is a life-threatening form of the disease (Mackinnon et al., 2005).

Sporozoites of malaria parasites ensure the endurance of their host cell by preventing apoptosis and inflammation by interfering with the host cell NF-kB pathway (Sicard et al., 2011; Singh et al., 2007) and hence several genes involved in the inflammatory response (Singh et al., 2007). The parasite also inhibits STAT3, which activates a wide variety of genes that control cell proliferation and survival and whose absence inhibits the acute phase response associated with infections (Alonzi et al., 2001). Angiotensin-converting enzyme 2, a SARS-CoV-2 receptor, is upregulated by IL-6 through STAT3 signalling (Mokuda et al., 2020). IL-6, which is crucial for cytokine storm development, is also down-regulated by the parasite (Pied et al., 1992). Both exoerythrocytic forms (EEFs) and erythrocytic stages of malaria use the same strategies to ensure parasite expansion (Singh et al., 2007). Other main gene upregulated by Plasmodium is *TMPRSS*, which encodes a serine protease needed for SARS-CoV-2 entry into the host cell (Zupin et al., 2020).

Apart from these pathways, the parasite promotes PD-1 expression in T cells with cell-extrinsic immunosuppressive functions. Programmed cell death protein 1 (PD-1) is a protein on the surface of cells expressed on activated T cells, B cells, and monocytes that regulates the immune response promoting self-tolerance, suppressing T cell inflammatory activity and likely regulating these cell types (Agata et al., 1996). Overexpression of PD1 on T cells is one of the indicators of T cell exhaustion (e.g. in chronic infection) (Pauken and Wherry, 2015). PD-1 reduces PKC/NF-kB signalling and IL-2 production and induces the expression of ubiquitin ligase E3 that leads to NF-kB degradation and T cell receptor (TCR) internalization (Karwacz et al., 2011). This down-regulation of the immune response may be an essential mechanism that controls T cell responses and might limit severe inflammation in patients with malaria and potentially other acute infections, such as COVID-19. It is though SARS-CoV-2 increases PD-1 expression (Schön et al., 2020).

4. Caspase-12

Inflammasomes are large macromolecular complexes involved in inflammatory response regulation. They are key signalling platforms that detect pathogenic microorganisms and sterile stressors and activate the highly pro-inflammatory cytokines interleukin-1β (IL-1β) and IL-18 (Latz et al., 2013; Labbé et al., 2010). They trigger inflammation by activating, on the one hand, caspase-1 and other caspases that cleave pro–IL-1β and pro–IL-18 into their mature active forms, and on the other hand, NF-kB pathway (Labbé et al., 2010) that results in pro-inflammatory cytokines release (Li et al., 2020). Caspase-12 is a second member of the caspase-1 subfamily that is catalytically inactive in humans; it acts as an inhibitor of both inflammasome and NF-kB pathways (Labbé et al., 2010). Expression of human caspase-12 is predominantly confined to African descent (Fig. 1) and is associated with dampened pro-inflammatory cytokine production and sepsis-related mortality (Saleh et al., 2004). Labbé et al. elegantly showed the role of caspase-12 in suppressing inflammatory response to malaria. Caspase-12 limited the immune control of parasite replication and dampened hyperinflammation. Experiments revealed that caspase-12 deficiency causes hyperactivation of NF-kB and enhances IFN-gamma production. As regards mechanism, caspase-12 competes with the NF-kB essential modulator (NEMO) for association with the inhibitor-kB (IkB) kinase (IKK)-α/β, effectively preventing the formation of the IKK complex and inhibiting downstream transcriptional activation by NF-kB (Labbé et al., 2010).

DNA Source	*n*	Stop TGA	Stop/Arg (T/C)GA	Arg CGA
Caucasian	187	187	0	0
Asian	160	160	0	0
South African	153	120	31	2
African American	623	499	113	11
TOTAL	1123	966	144	13

Fig. 1. Sequence analysis of more than 1100 genomic DNA samples from people of distinct ethnic backgrounds showed that most encoded the truncated prodomain-only form of caspase-12 (Csp12-S). The less-frequent CGA (Arg) polymorphism resulting in a full-length caspase polypeptide (Csp12-L) was found only in populations of African descent and was absent in all Caucasian and Asian groups tested.

5. Leukocyte-associated immunoglobulin-like receptor-1

Leukocyte-associated immunoglobulin-like receptor-1 (LAIR-1) is a member of the immunoglobulin superfamily (Meyaard et al., 1997) that inhibits T cell activation (Ravetch and Lanier, 2000). LAIR-1 is expressed on lymphoid and myeloid cells, monocytes, and immature CD34+ progenitor cells (Hammad et al., 2020). It is also described in alveolar macrophages (Houben et al., 2013). LAIR-1 suppresses neutrophil tissue migration and acts as a negative regulator of neutrophil-driven airway inflammation in lung diseases, such as bronchiolitis in respiratory syncytial virus (RSV) (Kumawat et al., 2019). Qin et al. collected blood neutrophil gauge test data of 2976 patients who have been diagnosed with SARS-CoV-2 at Wuhan Huoshenshan Hospital in Wuhan, China. They found that disease deterioration is related to the increase in the abundance and proportion of neutrophils. The percentage of neutrophils and the absolute value of neutrophils in patients with critical illness and death were always higher than those of non-critically ill patients and surviving patients. This indicates that continued excessive activation of neutrophils plays a crucial role in SARS-CoV-2, leading to severe illness and death (Qin et al., 2020).

Likewise, COVID-19 patients who have died had a significantly higher neutrophil to lymphocyte ratio (NLR). NLR was thus positively correlated with death (Pakos et al., 2020).

Achieng et al. discovered that low transcript expression of *LAIR-1*is associated with enhanced susceptibility to malaria anaemia and severity. Blockade of the LAIR-1 inhibitory signal by *Plasmodium*was also associated with enhanced NF-kB activation and cytokine production (Achieng et al., 2019). The p65 subunit of NF-kB, constitutively expressed in the nucleus of immune system cells, is retained in the cytoplasm (i.e. inactive form) upon engagement of LAIR-1. This was already evident eight hours after LAIR-1 occupancy. Moreover, a reduction in IkBα phosphorylation, the active form of the NF-kB inhibitor, was observed after LAIR-1 engagement (Poggi et al., 2000).

LAIR-1 activation decreases the boosting levels of critical components of the canonical T cell signalling pathway, including the three MAP kinases ERK1/2, JNK1/2, and p38. All three activate IL-2 gene and promote cellular proliferation (Genot et al., 1996; Park et al., 2020), affecting cell development and inflammatory cascades by intervening with the PI3K-AKT pathway. LAIR-1 also inhibits the production of IFN-1 (Martínez-Esparza et al., 2019).

Activation and increased levels of NK cells have been shown in COVID-19 (Masselli et al., 2020).

LAIR-1 in NK cells delivers a potent inhibitory signal that is capable of inhibiting target cell lysis by resting and activating NK cells (Meyaard, 2008). In primary B cells, LAIR-1 leads to decreased cytokine production (Merlo et al., 2005).

Finally, LAIR-1 suppresses cell growth by inhibiting the PI3K-AKT-mTOR axis. LAIR-1 is also involved in mRNA processing through its interaction with several eukaryotic translation initiation factors (i.e. eIF4E1B, eIF2S3, eIF3D, eIF4G2, eIF5B) and eukaryotic translation elongation factors (i.e. eEF1A2 and eEF1B2). The mechanisms involved may include LAIR-1 regulation of protein synthesis at the translational level or its action as a modulator that suppresses the PI3K-AKT-mTOR pathway directly (Liu et al., 2020).

Pieper et al. (2017) reported that up to 10 % of people living in malaria endemic regions produce antibodies that contain LAIR-1, suggesting a public antibody response. However, less than 1 % of European individuals these antibodies (Fig. 2). High levels of LAIR-1-containing antibodies dominate the response to infection without conferring enhanced protection against febrile malaria. Although LAIR-1 prevalence observed in African individuals may have been promoted by malaria infection, the data suggests that it is the exposure to the malaria parasite that selects the rare LAIR-1 B cells Pieper et al. (2017).

6. Glycophorins

Glycophorin A and glycophorin B are red blood cell surface proteins; they are both receptors for the parasite *Plasmodium falciparum*, which is the principal cause of malaria in sub-Saharan Africa (Jaskiewicz et al., 2019). DUP4 is a complex structural genomic variant that carries extra copies of a glycophorin A-glycophorin B fusion gene (Algady et al., 2018) and reduces the risk of severe malaria by up to 40 %. DUP4 is common in Kenyan populations, with allele frequency reaching 10 % (Band et al., 2015). DUP4 variant reaches a frequency of 13 % in south-eastern African populations and is restricted to East African populations (Algady et al., 2018). This variant that reduces the risk of severe malaria by 40 % has recently increased in frequency in parts of Kenya, yet it appears to be absent in West Africa (Leffler et al., 2017).

GYPA/B are involved in viral entry into the host cell and leukocyte migration, according to the GeneCards database (Genecards, 2020). They are receptors of several viruses for host invasion. It has been reported that several viruses bind to glycophorin proteins for penetration into the cell, including influenza virus, hepatitis A virus, rotavirus, parvovirus, Sendai virus, reovirus, and encephalomyocarditis (EMC) virus (Genecards, 2020; Gekker et al., 2018; Sciencedirect, 2020). According to *The Human Protein Atlas*, GYPA/B are mainly expressed in bone marrow, erythrocytes, neutrophils, lungs, lymphoid tissues, B- and T-lymphocytes, monocytes, spleen, and kidneys. As such, malaria might protect patients against SARS-CoV-2 infection by damping regular virus-host recognition through GYPA/B.

7. Conclusions

Multiple genetic and immunologic factors may be involved in the severity of COVID-19 in African individuals compared with the rest of the global population. These factors include direct actions of *Plasmodium falciparum* in the pathogenesis, expression of caspase-12, higher levels of LAIR-1-containing antibodies, and differential glycophorins expression. Other hypotheses can be added to this, such as chloroquine and its derivative drugs used for malaria, precarious data collection, ACE2 polymorphisms and other genes, and so on.

Knowledge of these pathophysiological mechanisms can help identify target points for drugs and vaccines development against COVID-19.

To our knowledge, this is the first study exploring the link between these variables and proposing a biological and molecular answer to the epidemiologic discrepancy in COVID-19 in Africa.

	n	IgG	IgM	Monoclonal LAIR-1
Tanzanian	112	6 (5.4%)	2-4%*	52*
Malian	656	57 (8.7%)	2-4%*	52*
European	1043	3 (0.28%)	4 (0.38%)	0

Fig. 2. Prevalence of LAIR-1-containing antibodies in South-eastern African versus Europe.
*Sources together.

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Declaration of Competing Interest

The authors report no declarations of interest.

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