



Review

SARS CoV2 infection _The longevity study perspectives

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ABSTRACT

Like other infectious diseases, COVID-19 shows a clinical outcome enormously variable, ranging from asymptomatic to lethal. In Italy, like in other countries, old male individuals, with one or more comorbidity, are the most susceptible group, and show, consequently, the highest mortality, and morbidity, including lethal respiratory distress syndrome, as the most common complication. In addition, another extraordinary peculiarity, that is a surprising resistance to COVID-19, characterizes some Italian nonagenarians/centenarians. Despite having the typical COVID-19 signs and/or symptoms, such exceptional individuals show a surprising tendency to recover from illness and complications. On the other hand, long-lived people have an optimal performance of immune system related to an overexpression of anti-inflammatory variants in immune/inflammatory genes, as demonstrated by our and other groups. Consequently, we suggest long-lived people as an optimal model for detecting genetic profiles associated with the susceptibility and/or protection to COVID-19, to utilize as potential pharmacological targets for preventing or reducing viral infection in more vulnerable individuals.

1. Introduction

The new Coronavirus SARS CoV2 infection (COVID-19) is characterized by a wide range of manifestations from asymptomatic to the severe. Lethal respiratory distress syndrome is the most frequent

complication, characterized macroscopically by an evident differential gender and age susceptibility (Asfahan et al., 2020; Bonafè et al., 2020; Fuellen et al., 2020; Renu et al., 2020). Growing literature data are also reporting diverse factors influencing the infection's outcome. Among these, a major or minor expression of Angiotensin Converting Enzyme 2

Abbreviations: ACE, angiotensin-I converting enzyme; ACE/DD, polymorphism of the angiotensin converting enzyme; ACE2, angiotensin converting enzyme 2; ADAM-17, metalloproteinase domain 17; Ang, angiotensin; aPTT, partial thromboplastin time; ARDS, acute respiratory distress syndrome; AT1R, activity of angiotensin 1 receptors; AT2R, activity of angiotensin 2 receptors; BMI, body mass index; CCR5Δ32, genetic variant of chemokine receptor; COVID-19, Coronavirus disease 2019; Cox 2, cyclooxygenase 2; CpGs, CpG islands; D, deletion; DBP, diastolic blood pressure; DCs, dendritic cells; DIC, disseminated intravascular coagulation; DUSP1, dual specificity phosphatase 1; EC, endothelial cells; EH, essential hypertension; ET-1, endothelin-1; FDP, fibrin degradation products; FGF21, fibroblast growth factor 21; FluAV, influenza A virus; HDACs, histone deacetylases; HIV-1, human immunodeficiency virus-1; hPIV2, human parainfluenza virus type 2; HSPs, heat shock proteins; I, insertion; IFN-γ, interferon-γ; INR, international normalized ratio of the prothrombin time; IP-10, IFN-γ-Inducible Protein 10; LPS, lipopolysaccharide; 5-LO, lipoxygenase 5; MAPK, mitogen-activated protein kinase; MKP-1, mitogen-activated protein kinase phosphatase-1 (); MCP1, monocyte chemoattractant protein-1; MI, myocardial infarction; Mphi, human macrophages; NAD, nicotinamide adenine dinucleotide; NF-Kb, nuclear transcription factor κB; NK, natural killer; NO, nitric oxide; ORF, open reading frame; PAI-1, plasminogen activator inhibitor-1; PC, prostate cancer; PCR, Polymerase Chain Reaction; PD, protease domain; PT, prothrombin time; PTMs, post-translational modifications; RANTES, regulated upon activation, normal T cell expressed and secreted; RAS, renin-angiotensin aldosterone system; RBD, receptor-binding domain; RFLP, restriction fragment length polymorphism; ROS, reactive oxygen species; RSV, respiratory syncytial virus; SARS CoV2, severe acute respiratory syndrome Coronavirus 2 virus; SARS-1, severe acute respiratory syndrome virus 1; SBP, systolic blood pressure; SIRT-1, Sirtuin 1; SNP, single nucleotide polymorphism; SSCP, single strand conformation polymorphism; ssRNA, single-stranded RNA; T2DM, type 2 diabetes mellitus; TGF-β, transforming growth factor beta; Th1, t-helper lymphocyte type 1; TLR4, toll-like receptor 4; TNFR, tumor necrosis factor receptor; TNF-α, tumor necrosis factor-α.

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(ACE2) (Bourgonje et al., 2020; La Vignera et al., 2020; Peron and Nakaya, 2020) the strength of inflammatory response (Amiral et al., 2020; Bonafè et al., 2020; de Lucena et al., 2020), and the presence of comorbidities in infected patients (i.e. essential hypertension, diabetes mellitus and obesity) (Aggarwal et al., 2020; Asfahan et al., 2020; Jackson-Morris et al., 2020; Huizinga et al., 2020; Zaim et al., 2020) have suggested as COVID-19 predominant drivers. Such COVID-19 infection features lead to speculate the crucial role of individual genetic background in this infection, rather than in others. In addition, another interesting COVID-19 peculiarity stays in the related mortality stratified for age, as reported by Italian National Statistics Institute (<https://www.epicentro.iss.it/Coronavirus/sars-cov-2-decessi-italia#2>). Accordingly, the mean age of patients, dead and positive for SARS-CoV-2, is 80 years (median 82, range 0–109, Inter Quartile Range - IQR 74–88). The median age of SARS-CoV-2 positive deceased patients is more than 25 years higher than that of patients with contracted infection (median age: patients who died 82 years - patients with infection 56 years). The most consistent mortality excess (> 60 % between January and April) is observed among men belonging to 70–89 age group. Women, dead after contracting SARS-CoV-2 infection, are older than men (median age: women 85 - men 79). In females >90 years old Italian population, the COVID-19 absolute number of deaths is higher than in males. Such is not surprising, by considering that females constitute the large majority of the 90 years-old population. The excess of mortality during the SARS-CoV-2 epidemic peak in the >90 years old population is similar between the two genders. Males achieve an increase of 53 % mortality excess, and females of 46 % respect to the average for the years 2015–2019 (https://www.epicentro.iss.it/Coronavirus/pdf/Rapp_Istat_Iss_9luglio.pdf).

Since metabolic disease and disabilities are most frequent in very aged women (Gordon and Hubbard, 2020; Hoogendijk et al., 2018) respect to men, it is not surprising that mortality excess of over 90 females is almost like men. In addition, these data lead likely to suppose that this trend may be linked to crucial role of a different genetic background asset, in both COVID-19 predisposition and prognosis (Cai, 2020; Sharma et al., 2020).

Other factors, beyond genetic background asset, have been suggested as potential causes of this trend. Of note are the data derived from a study performed by a group of researchers from the Johns Hopkins University (Sharma et al., 2020). They have stressed the gender differences between men and women as another plausible reason, including, among these, higher contribution of pre-existing illnesses (i.e., cardiovascular diseases, hypertension, T2DM, and chronic lung disease), higher risk behaviors (i.e., smoking and alcohol use), and occupational exposure in man than women. Other causes are, however, linked to biological characteristics, such as the sex hormones (i.e., estrogens, progesterone, and androgens) able to regulate in a differential manner the immune system between the sexes (Sharma et al., 2020). In addition, women are expression of functional mosaics of genes located on X chromosomes, and many immune-related genes map on X chromosomes (Sharma et al., 2020). Women usually have stronger innate and adaptive immune responses than men, that result in a faster clearance of pathogens and greater vaccine efficacy, even if this contributes to their higher susceptibility to inflammatory and autoimmune diseases (McClelland and Smith, 2011).

In the complex, three unique elements, in part abovementioned, emerge on COVID-19, that might constitute object of original investigations: i) the role of genetic background asset, ii) age and iii) and gender of the host (Márquez et al., 2020; Schröder, 2020). About these three features, our team, in the last 20 years and, as attested by the numerous studies performed (widely quoted in Balistreri et al., 2012), has experienced the different aspects on the role of genetic variability of key molecules involved in the regulation of the immune-inflammatory response related to onset and progression of age-related multifactorial pathologies, infectious diseases included, as well as in the rate of life span expectancy and longevity (data described in Balistreri et al., 2012).

Interesting results report our studies, and particularly about centenarians, who represent the optimal study's model in our research (widely quoted in Balistreri et al., 2012). They are equipped to achieve extreme limits of human life span and to escape fatal age-related diseases, such as cardiovascular diseases and cancer (Garagnani et al., 2013; Ostan et al., 2016; van den Berg et al., 2019). Proven data have led us to suggest that longevity is the excellent result of an optimal performance of immune system related to an overexpression of anti-inflammatory variants in immune/inflammatory genes (Balistreri et al., 2012; Hook et al., 2018; Pilling et al., 2016; Ukraitseva et al., 2016; van den Berg et al., 2019; Villa et al., 2015). However, we and other groups have also demonstrated that, beyond genetics, epigenetic, stochastic, and environmental factors, such as the diet, play a crucial role in ageing and longevity (Moskalev et al., 2014; Longo et al., 2015; Balistreri, 2018; Scola et al., 2019). In this view, the reduced mortality excess in >90 years old males respect to age-matched females (Marcon et al., 2020), prompt us to speculate that data acquired on genetics of longevity might be useful in searching genetic profiles associated with the susceptibility and/or protection from COVID-19.

Here, published data on the COVID-19 etiopathogenesis and heterogeneity of the manifestations have discussed by considering the expertise acquired on genetic determinants of longevity to suggest new perspectives and approaches both in the diagnostic/therapeutic field, and in prevention.

2. Genetics of ACE2 and Longevity: relevance in SARS COV-2 susceptibility

Discovered as a part of the renin-angiotensin system (RAS), an important regulator of blood pressure homeostasis, the ACE2 is believed to have a role in blood pressure regulation and cardiac functionality (Groß et al., 2020; Liu et al., 2020; Devaux et al., 2020). ACE2 is a type I transmembrane glycoprotein with 805 amino acids, having a single extracellular catalytic domain represented by the N-terminal portion with the claw-like protease domain (PD), and a C terminal domain referred as the collectrin-like domain. ACE2 acts as a zinc metalloproteinase, and precisely, it hydrolyzes Angiotensin (Ang) I in Ang 1-9 and Ang II into Ang 1-7 (Donoghue et al., 2000). In addition, its C-terminal domain, a homolog of a renal protein, collectrin, makes ACE2 a protein with multiple and characteristic physiological functions. They range from the function of regulator of RAS (through the ACE2-Ang-(1-7)-Mas axis) to anti-inflammatory and antifibrotic effects on the respiratory system and anti-inflammatory, antioxidative stress, and protective effects on vascular function, and yet protective action against myocardial fibrosis, nephropathy, pancreatitis, and insulin resistance (Donoghue et al., 2000). In addition, trans-membrane localization assigns to ACE2 additive functions, including the role of amino-acid transporter and regulator of gut dysbiosis and vascular permeability. Moreover, ACE2 is expressed in various tissue districts, including the vascular system (endothelial cells, migratory angiogenic cells, and vascular smooth muscle cells), heart (cardiomyocytes, endothelial cells, pericytes, and epicardial adipose cells) and kidneys (glomerular endothelial cells, podocytes and proximal tubule epithelial cells), liver (cholangiocytes and hepatocytes), retina (pigmented epithelial cells, rod and cone photoreceptor cells and Müller glial cells), enterocytes of the intestines, circumventricular organs of the central nervous system, upper airway (goblet and ciliated epithelial cells), and alveolar (Type II) epithelial cells of the lungs and pulmonary vasculature (Bourgonje et al., 2020; Donoghue et al., 2000; Devaux et al., 2020; Groß et al., 2020; La Vignera et al., 2020; Liu et al., 2020; Peron and Nakaya, 2020). Its multiple actions and localization explain the complex symptomatology of COVID-19, since SARS COV2 virus hijacks ACE2 as preferential receptor, by binding its receptor-binding domain (RBD) with PD domain and forming the RBD-PD complex (Fig.1). This determines loss of ACE2 function, by endocytosis of the enzyme along with SARS COV2 viral particles. In turn, such provokes

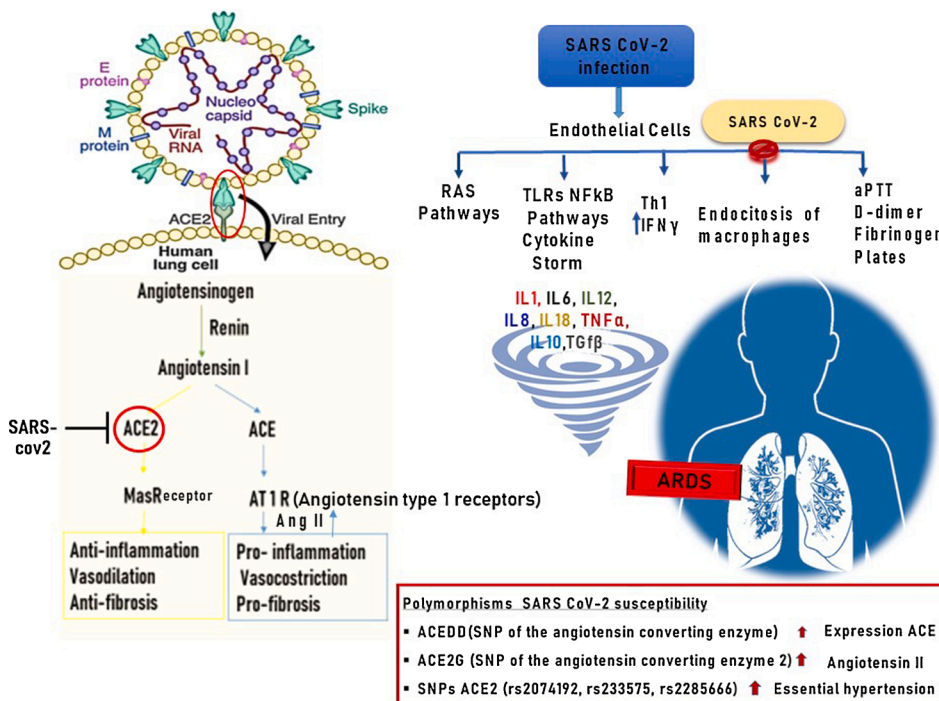


Fig. 1. SARS CoV-2 infects epithelial cells by recognizing ACE 2 receptor, which release a cytokine storm and induce activation of cascade coagulative. Hyper-activation of proinflammatory response causes acute respiratory stress syndrome (ARDS). The box indicates some of the ACE and ACE2 SNPs, that have been demonstrated to play a decisive role in susceptibility to SARS COV-2. ACE = angiotensin-I converting enzyme ; ACE/DD = polymorphism of the angiotensin converting enzyme 2; Ang2= angiotensin 2; aPTT = partial thromboplastin time; AT1R = activity of angiotensin 1 receptors ; MasR = endogenous orphan receptor; Mphi = human macrophages; PLT = platelets; RAS = renin-angiotensin aldosterone system.

elevation of Ang II levels accompanied by an increased activity of angiotensin 1 receptors (AT1R) at the cost of ACE2/ Ang 1–7 driven pathway, that induces fibrosis, hypertrophy, increased reactive oxygen species (ROS), vasoconstriction, and gut dysbiosis (Bourgonje et al., 2020; Devaux et al., 2020; Groß et al., 2020; La Vignera et al., 2020; Liu et al., 2020; Peron and Nakaya, 2020). In addition, an increase of TNF- α (tumor necrosis factor- α) and activation of its tumor necrosis factor receptor (TNFR) occur. These last, in combination with the comorbidities of infected individuals, such as diabetes mellitus (T2DM) and hypertension, can evoke a cytokine storm with devastating effects (Coperchini et al., 2020; Gubernatorova et al., 2020; Nile et al., 2020).

Furthermore, it has been demonstrated a differential balance of the RAS pathway between the two sexes (Evans et al., 2000; Kang and Miller, 2002; Reckelhoff, 2001; Sandberg and Ji, 2003). In men, the ACE/AngII/AT(1)R pathways are boosted, while in women RAS is prevalently regulated by the ACE2/Ang(1-7)/MasR and AT(2)R pathways. Evidence obviously reports that premenopausal women than aged-matched men have a lower incidence to onset of renal and cardiovascular diseases, likely linked to differential control of the RAS between the two sexes. With advancing age, the female cardiovascular protection is highly reduced because of low levels of estrogens in post-menopause. However, the probable contribution of other sex hormones needs to be further examined (Evans et al., 2000; Kang and Miller, 2002; Reckelhoff, 2001; Sandberg and Ji, 2003; Sharma et al., 2020). Another aspect of interest stays in differences of the frequency between the two sexes of polymorphisms in RAS genes (O'Donnell et al., 1998; Reich et al., 2003; Lu et al., 2012), accompanied by progressively more reported sex-specific associations between hypertension and RAS gene polymorphisms. In men, ACE and AT1R gene polymorphisms are significantly associated with hypertension, while in women *angiotensinogen* and ACE2 gene polymorphisms are associated with hypertension. Such suggests the presence of sex differences in responses to the RAS from the birth. The most widely studied polymorphisms in the *angiotensinogen* gene are M235T and T174M (Mohana et al., 2012). Mohana and coworkers (Mohana et al., 2012) have observed an increased frequency in specific genotypes of these SNPs in hypertensive females than normotensive females. Such data evidence an increased risk to onset of hypertension in female carriers of these genotypes. The T174M

polymorphism, determining a threonine substitution to methionine in the codon 235, has been showed in female carriers of heterozygous TM genotype (one copy encoding for threonine and one copy encoding for the substituted methionine) to raise the risk to hypertension for a 2.48-fold, when compared to carriers of both homozygous genotypes (TT + MM). Interestingly, no differences have been observed in frequency of any genotype between hypertensive and normotensive males (Mohana et al., 2012).

However, an interindividual heterogeneity in the prognosis of COVID-19 infection has been also reported, enough to start talking on ACE2 as a potential foe and not as a strong friend of such virus, that might potentially be related to a heterogeneous expression of ACE2 and/or likely to not uniform function of ACE2 among people (Dalan et al., 2020). Both are the result of the effects of genetic variants in ACE2 gene (Devaux et al., 2020), discovered by Tipnis and Donoghue 's groups (Donoghue et al., 2000; Tipnis et al., 2000), and located on Xp22 chromosome in a particular region that escapes by X chromosome inactivation. According to variability of ACE2 functions or expression, strong biological evidence from animal models has demonstrated the ACE2 gene as a key regulator of blood pressure (Donoghue et al., 2000; Tipnis et al., 2000). However, the human genetic literature reports contrasting data on an eventual relationship between ACE2 variants and blood pressure (Gurley et al., 2006) (Table 1). Interestingly, Malard and coworkers (Malard et al., 2013) observed two significant associations of rs2074192 and rs233575 ACE2 variants in European males and females. Precisely, their results evidenced that the major allele of rs2074192 and the minor allele of rs233575 in ACE2 gene significantly increased systolic blood pressure (SBP) and diastolic blood pressure (DBP) in European males, and significantly induced SBP changes in European females. Likewise, in Chinese population none of the ACE2 polymorphisms has been demonstrated to be significantly associated with essential hypertension (EH) in the male group. In the female group, the results revealed a significant difference between the genotype distributions and allele frequencies of 5 variants (rs1514283, rs2285666, rs4646155, rs4646176, and rs879922) located in the introns of ACE2 gene by comparing the EH group with normotensive (NT) group (Zang et al., 2018). The data above described also explain the association of ACE2 with the onset of hypertension, kidney diseases, and T2DM. On the other

Table 1

RAS polymorphisms as risk factor specific for age-related pathologies that can be involved in inflammatory response to SARS Cov2. The new coronavirus contacts the host cells through ACE2, a key enzyme of the RAS pathway, which is therefore being studied for the understanding of viral infection and for possible vaccination and therapeutic interventions. The ACE2 gene has nucleotide variants which could affect the functionality or conformation of the protein product, also influencing the approach of the virus with the host organism. As observed, none of the ACE2 variants positively or negatively modifies the link with SarS Cov N protein As is known, the presence of age-related diseases (especially hypertension) is a risk factor for the severe evolution of SarS Cov2 infection. Various polymorphisms of ACE and ACE2 have been analyzed in various groups of population outlining a profile of frailty or protection that could affect the response to Covid 19. (EH: Essential Hypertension).

GENE	POLYMORPHISM	GENOTYPE	ASSOCIATION	POPULATION	REFERENCE
ANGIOTENSINOGEN	rs4762 G/A	GA	EH	Caucasian	Mohana et al. (2012) Malard et al. (2013) Zhang et al. (2018) Lu et al. (2012)
	rs2074192 G/A	G/*		Caucasian	
	rs 233,575 T/C	C/*			
	rs1514283 T/C	C/*			
	rs4646155 C/T	T/*	EH	Asian	
	rs4646176 C/G	G/*			
	rs879922 C/G	C/*			
	rs2285666 G/A	G/G			
	rs961360700 C/T	C/T	Negative association with Infection SARS COV2	Caucasian African Asian	Othman et al. (2020)
	rs143936283 T/C	T/C			
	rs146676783 C/T	C/T			
	rs759579097 C/T	C/T			
	rs370610075 C/A	C/A			
	rs766996587 C/A,T	C/A,T			
	rs73635825 A/G	A/G			
ACE 2	rs781255386 T/C	T/C	Negative association with Infection SARS	Asian	Itoyama et al. (2005)
	rs228566 A//G	A/G			
		DD	EH	Chinese	Yang et al. (2006)
		D/*-DD	T2DM	Chinese	Xu et al. (2012)
		I/I	Disability	Caucasian	Seripa et al. (2011)
		DD	Longevity	Caucasian	Schachter et al. (1994) Nacmias et al. (2007)
ACE	rs1799752 D/I				
AT1R	rs5186 A/C	C/*	EH	Caucasian	Liu et al. (2015)
ACE/ACE2	ACE rs1799752	ACEDD/ACE2GG	EH	Asian	Pinheiro et al. (2014)
	ACE2 rs2285666 G/A			Caucasian Afro/Hispanic	

hand, the G8790A (rs2285666) single nucleotide polymorphism (SNP) in ACE2 gene has been, indeed, related to a significant risk of hypertension, T2DM stroke etc. in Chinese population (Wu et al., 2017). Furthermore, a recent meta-analysis performed in 2019 by a Brazilian research's group has demonstrated that ACE2 G8790A polymorphism is individually not associated with the risk to develop systemic arterial hypertension (SAH), but the combination of ACE DD genotype with ACE2 G allele significantly rises the disease's susceptibility in female people (OR = 3.6, $p = 0.03$), and mainly with a stronger susceptibility in DD/GG carriers (OR = 7.1, $p = 0.01$) (Pinheiro et al., 2019). Precisely, the analysis of the combined genotypes of the two genes evidenced a significant association of the combined ACEDD genotype with ACE2 GG genotype (DD/GG) in female individuals. The combined DD/GG genotype conferred a statistically significant higher risk (>7 times) to the onset of hypertension than individuals carrying the II/GG genotype, after adjustment for confounding factors, including age (old people and young), dyslipidemia (presence and absence), body mass index (BMI; obese and non-obese), smoking and alcohol consumption (Pinheiro et al., 2019). In contrast, male subjects showed no significant associations. The results obtained in this study indicate that the combination of genetic polymorphisms in ACE and ACE2 genes can contribute to the development of hypertension (Pinheiro et al., 2019). In another study, it has been also reported the associations of ACE D allele or DD genotype with T2DM, suggesting the involvement of overactivated RAS (by the increased activity of ACE in D carriers) in dysmetabolism and underlying the contribution of proinflammatory substrates to SARS infection onset (Xu et al., 2012). Another important datum has been provided from the study of Seripa and coworkers (Seripa et al., 2006). Precisely, it reports uniform D allele frequencies in individuals of the various groups of age, centenarians included. This finding is consistent with a lot of studies that have failed to replicate the association previously reported from Schachter and colleagues on increased ACE frequency in longevity (Schachter et al., 1994). After adjustment for sex, however, the study showed a significant association between the D allele and centenarian

age, consequently suggesting a sex-dependent involvement of ACE alleles with longevity (Seripa et al., 2006).). The findings attained have also suggested that old age individuals with the ACE and ACE2 DD/G genotype and more pronouncedly DD/GG individuals present a greater susceptibility to dyslipidemia and might be independent risk factors for hypertension in the sample analyzed (Seripa et al., 2006). In addition, the results of the studies, here reported, also allow us to assume that DD/G- carriers would have an enhanced activity of ACE (DD genotype) in combination with the reduced ACE2 activity (G allele), since ACE2 G allele appears to cause a reduction in the activity of this enzyme. Despite the clear-cut evidence about the effect of genetic variants in ACE and ACE2 genes, no data exist at this moment on the role of ACE2 SNPs in SARS COV2 susceptibility or protection. At this date, no evidence on relationship between ACE2 polymorphisms and COVID-19 susceptibility or protection has been published (Devaux et al., 2020). However, genetic variations in ACE2, have been evaluated in susceptibility to severe SARS-CoV or development of SARS. By cloning the full-length cDNA of the ACE2 gene in the lung, where replication occurs on SARS-CoV, it has been shown that there are different splicing sites. Non-synonymous nucleotide substitutions and other variations with a minor allele frequency higher than 0.05 have been genotyped in all SARS cases, contacts, and noncontacts (Itoyama et al., 2005). This case control study, involving 44 SARS cases, 16 anti-SARS-CoV antibody positive contacts, 87 antibody-negative contacts, and 50 non-contacts in Vietnam, failed to obtain associations of ACE2 gene polymorphisms with the disease process in the population studied. Nevertheless, identification of new 5'-untranslated exon and new SNPs has been considered helpful in investigating the regulation of ACE2 gene expression in the future. More recently, Othman and coworkers have investigated eight common variants in hACE2 gene that map in the extracellular domain. The results obtained demonstrated that none of these variants affect the binding energy score of ACE2 PD domain with the viral spike RBD of SARS-CoV-2. On the contrary, the acquired amino acid residue mutations Q493 and P499 of SARS-CoV-2 RBD are crucial for binding to

human ACE2 and maintaining the stability of the interface (Othman et al., 2020).

3. Genetic determinants of innate immunity and longevity. Relevance for SARS COV-2 immunopathogenesis

According to evolutionary ageing theories, the major part of parameters influencing immunosenescence appear to be under genetic control (Capri et al., 2008; Ostan et al., 2008; Troen, 2003; Candore et al., 2006a). An example is given by the innate immune system, involved in neutralizing infectious agents (Candore et al., 2006b, 2006c). It plays a beneficial role until the time of reproduction and parental care. In old age, a period largely not foreseen by evolution, it can determine an opposite and detrimental effect through chronic inflammatory responses ("antagonistic pleiotropy") (Williams, 1957). Genetic pro-/anti-inflammatory variations in innate immune response are, indeed, assumed to influence the susceptibility to age-related human diseases, by altering host response to environmental and endogenous stress (Vasto et al., 2007). Thus, they can determine a negative or positive control of inflammation, by affecting both interactions between host and microbes and survival of the individual and attainment of longevity.

A characteristic enigma of longevity is the gender and the social phenomenon of "feminization of old age" (Candore et al., 2006a; Capri et al., 2008; Balistreri et al., 2012). The demographic and social changes of the past decades, responsible for longevity and the improvements in public health, have created new, and often very dissimilar realities for women and men. People are all aware that they differ in their anatomy and physiology, but also in more complex traits, such as lifespan (in Europe, 78.2 years for men and 83.7 years for women, respectively) (https://ec.europa.eu/eurostat/statistics-explained/index.php/Mortality_and_life_expectancy_statistics#Life_expectancy_at_birth_increased_in_2017_only_for_men) and mortality. No conclusive explanation for these new differences until now does report (May, 2007; Perig-Chiello and Hutchison, 2010). An intricate interaction of environmental with social structural, behavioral (i.e., the complex pattern of roles and values that define what is thought as masculine and feminine) and genetic factors have been suggested as the more probable cause (Candore et al., 2006a; Capri et al., 2008; Balistreri et al., 2012). From a genetic perspective, our suggestion based on the studies in Sicilian population supports a female-specific gene-longevity association (data widely reported in Balistreri et al., 2012), by emphasizing the paradoxical role of socio-cultural habits in female longevity. Precisely, our studies on Sicilian population demonstrated that an over-expression of anti-inflammatory CCR5Δ32 variant, +896 G (299Gly) TLR4 allele, -765 C Cox-2 allele, -1708 G and 21C 5-Lo alleles (Table 2) characterizes male centenarians (Balistreri et al., 2004, 2008; Listi et al., 2008; Balistreri et al., 2012). From a more general vision, the variability of genes playing a key role in innate and adaptive immune response appears both to be implied in the differential strategies used by the two sexes in achieving longevity, and in contributing to the preferential sex dimorphism of the age-related diseases (Lio et al., 2002a). Thus, male centenarians are people, who seem genetically equipped for defeating major age-related diseases. They present SNPs in the immune system genome (i.e., SNPs or other genetic variations, located within the promoter regions of proinflammatory cytokines) which, regulating the immune-inflammatory responses, may be associated with longevity (Balistreri et al., 2012). Consistent with this, it might be relevant that some genetic variants associated, in the different populations, with the longevity trait are more represented in male centenarians than in female. This leads to suppose that hormonal constellation of women could facilitate a long-life expectancy, whereas a more robust genetic background in men could help to achieve this goal. Intriguing data on genetic of longevity are focused on genes involved in immune response and susceptibility to SARS COV2. From our investigations in Sicilian population, TLR4, CCR5, Cox2, 5-Lo genes may be considered good examples

Table 2

The molecular profile of the factors of natural immunity could influence the outcome of an infection in the centenarians. The evolutionary success and survival of a species are undoubtedly linked to the efficiency of the immune response, first innate, then adaptive. To organize intense inflammatory responses were also those that could overcome infections and parasitic infestations. However, the inflammatory background in old age harms organic homeostasis and helps degenerative events. The centenarians seem to enjoy a moderately inflammatory, functional and balanced response towards modest microbial loads. The SNP variant of the TLR4 associated with a reduced NF-κB activity, is frequent precisely in the long-lived, whereas the allele variant (T/* of the SNP C1019 T) of Connexin 37 is reduced, which is associated in various studies on Asians and Caucasians. Myocardial infarction and carotid thickening. The chemokine receptor gene CCR5 also has a variant polymorphic related to functional receptor alteration (HIV) and resistance to the virus that is more frequent in centenarians; this once again suggests that structural and functional modulation of microbial receptors could play a key role in resistance to infectious agents.

GENE	POLYMORPHISM	GENOTYPE	ASSOCIATION	REFERENCES
TLR4	rs4986790 A/G	G/*	longevity	Balistreri et al. (2009)
CCR5	rs333 Del/Ins	Δ32*	HIV protection	Balistreri et al. (2007)
Connexin 37	rs1764391 C/T	C/*	longevity/protective	Listi et al. (2007)

(Balistreri et al., 2012). They provide an ideal model to understand the different implications of their genetic variants in the risk to age-related diseases, i.e., atherosclerosis, myocardial infarction (MI), Alzheimer disease, and prostate cancer, and reciprocally in increased chance to attain longevity (Balistreri et al., 2009). TLR4 gene (GenBank accession number: NM138554.1) codifies the best understood Toll Like Receptor (TLR) member, the TLR4, involved in recognition of LPS, the prototypic TLR4 ligand, and other exogenous and endogenous (i.e., HSPs, hyaluronic acid, b-defensin-2, ox-LDL, fibronectin, and amyloid peptide) ligands. TLR4 activation implies a downstream signaling mediated by several intracellular adaptor molecules and the consequent activation of transcription factors, such as NF-κB (Balistreri et al., 2009). This determines the production of different pro-/anti-inflammatory mediators. These lasts, such as IL-10, are produced by the parallel activation of anti-inflammatory pathways to limit the potential tissue damage from excessive activation of the innate immune system. SNPs modulate both TLR4 activity and function. In human, only two SNPs, +896A/G (Asp299Gly; rs4986790) and +1196 C/T (Thr399Ile; rs4986791), have a frequency > 5% (Arbour et al., 2000; Ferwerda et al., 2007, 2008). They induce a blunted response to LPS and are phenotypically associated with changes in the production of cytokines, principally those carrying the Asp299Gly variant (Arbour et al., 2000; Ferwerda et al., 2007, 2008; Balistreri et al., 2009). Accordingly, our and other studies suggest the ability of this SNP to modulate the risk to major age-related diseases and infections (widely quoted in Balistreri et al., 2009). On the other hand, pro-inflammatory responses are evolutionary programmed to resist to fatal infections. Thus, it is not surprising that the genetic background of people that survive to an advanced age may be protective against infections (Balistreri et al., 2009). In a recent study, we demonstrated that levels of IL-6, TNF-α, IL-10 and eicosanoids in LPS stimulated whole blood samples is influenced by TLR4 genetic polymorphisms (Balistreri et al., 2011). Both pro-inflammatory cytokines and eicosanoids were significantly lower in carriers bearing the +896 G TLR4 allele, whereas the anti-inflammatory IL-10 values were higher (Balistreri et al., 2011). This suggests the ability of the +896 G TLR4 allele to mediate a better control of inflammatory responses induced by chronic stimuli (Balistreri et al., 2011). Based on data reported herein, some suggestions may be drawn. First, pathogen load, by interacting with the host genotype, determines the type and intensity of inflammatory responses, according to the pro-inflammatory status and tissue injury, implicated in the patho-physiology of major age-related diseases. Second, adequate control of inflammatory response might reduce the risk of these diseases,

and, reciprocally, might increase the chance of extended survival in an environment with reduced pathogen load. Accordingly, a higher frequency of the anti-inflammatory +896 G TLR4 allele has been observed in centenarians (Balistreri et al., 2004). Our data in male Sicilian population confirm this suggestion and emphasize the role of antagonistic pleiotropy in ageing and longevity (Candore et al., 2006c; Balistreri et al., 2004; Incalcaterra et al., 2010; Balistreri et al., 2012). The CCR5 gene (number accession of GenBank: NM00579) codifies for a G protein-coupled chemokine receptor, the chemokine receptor 5 (CCR5), which regulates trafficking and effector functions of memory/effector Th1 cells, macrophages, NK cells and immature dendritic cells. CCR5 and its ligands are important molecules in viral pathogenesis (Balistreri et al., 2007). Recent evidence has also demonstrated the role of CCR5 in a variety of human diseases, ranging from infectious and inflammatory age-related diseases to cancer (Rautenbach and Williams, 2020). A notable variant of CCR5 gene is a 32 bp (Δ 32) deletion, which causes a frame shift mutation in exon 4 (CCR5 Δ 32; rs333) and determines stop protein maturation and loss of expression of functional CCR5 receptor. Regarding human immunodeficiency virus-1 (HIV-1) infection, it is well known that genetic polymorphism in CCR5, its coreceptor, influences the natural history of HIV-1 infection (Balistreri et al., 2007). The mutant allele CCR5- Δ 32 does not produce a functional protein and has been shown to protect host cells against HIV-1 infection, and progression into acquired immunodeficiency syndrome is delayed after seroconversion takes place (Balistreri et al., 2007). Virus receptors generally play a key role in the entry of the pathogen into the host cells and can influence development or progression of viral diseases. By analogy with the abovementioned concepts, we believe that genetic polymorphisms in metabolic pathways regulating ACE2 could influence SARS-CoV2 infection or clinical manifestations. Consistent with this, Li and co-workers (Li et al., 2020) have reported that in normal samples, the immune cells were not activated and the correlation between infiltration and ACE2 expression was not significant. After 48 h, virus activities, such as viral entry into the host cell, virus life cycle, and viral transcription, appeared enhanced. In addition, T-cell cytokine secretion was increased, and T-cell activation was stimulated. In particular, the high expression of ACE2 was related to innate immune responses, adaptive immune responses, B cell regulation and cytokine secretion, as well as an enhanced inflammatory response induced by IL-1, IL-10, IL-6, IL-8 (Li et al., 2020). Thus, it appears very probable that the immune system dysfunction involved in the high expression of ACE2 is related to the symptoms of a cytokine storm. A clinical study in Wuhan pointed out that the levels of IL-1 β , IL-10 and IL-8 were significantly increased in critically ill patients with new Coronavirus infection, indicating that the pathologic process may involve an exaggerated pro-inflammatory cytokine response (Tay et al., 2020). This may be related to pyroptosis, which has been suggested as another pathogenic mechanism involved in COVID-19 infection (Tay et al., 2020). Pyroptosis is an inflammatory form of apoptosis. The fact that tissue injury and death may be related to a pro-inflammatory process resulting from the viral infection suggests that the use of IL-1 β blockers or IL-18 blockers may have some benefit in COVID-19 patients. The activation of neutrophils, NK cells, Th17 cells, Th2 cells, Th1 cells, dendritic cells, TNF α secreting cells can be induced by overexpression of ACE2 leading to a severe inflammatory response (Tay et al., 2020).

4. Relevance of cytokines genetic determinants associated with longevity in COVID-19 management

Cytokines are considered key players in maintaining lymphocyte homeostasis (Iannitti and Palmieri, 2011; Sanjabi et al., 2009). Their function is not limited to induce response after an immune insult, but they can modulate the nature of response (cytotoxic, humoral, cell mediated, inflammatory or allergic) or, in contrast, can cause non-responsiveness and active immune suppression. For example, IL-6, promptly and transiently produced in response to infections and tissue

injuries, contributes to host defense through the stimulation of acute phase responses, hematopoiesis, and immune reactions (Gubernatorova et al., 2020). Although its expression is strictly controlled by transcriptional and posttranscriptional mechanisms, dysregulated continual synthesis of IL-6 is a key factor in the pathogenetic mechanisms of the Coronavirus infection (Russell et al., 2020). Accordingly, COVID-19 induces a pro-inflammatory generation and secretion of cytokines, such as IL-1 β and IL-6 via the TLRs-NF- κ B pathways, that cause lung inflammation, fever, and fibrosis. Anti-inflammatory cytokines, such as IL-1-Ra, IL-37 or IL-38 could potentially provide relief in both systemic inflammation and fever occurring after infection (Conti et al., 2020).

Concerning IL-6, the COVID-19 infection induces high levels of IL-6 for at least 2 weeks after disease onset (Gubernatorova et al., 2020). Children present lower levels of cytokine production. IL-6 has been also suggested as a potential prognostic marker of COVID-19 disease severity. It is, indeed, well recognized that the activation of NF- κ B leads to the increased proinflammatory cytokines, such as TNF- α , IL-6, and IL-1 β , which contribute to the activation of profibrotic transforming growth factor beta (TGF- β) pathway (Mahajan et al., 2019). In this scenario, IL-6 blood measurements appear as a powerful and useful tool to diagnose severe COVID-19 cases and evaluate their prognosis. The findings suggest that IL-6 may be used to estimate the severity of COVID-19. The optimum critical point of IL-6 in the groups studied is 24.3 pg/mL, which also represents the upper limit of no severe pneumonia (Gao et al., 2020). Consistent with these observations, different molecules related with the IL6 pathway have been suggested as potential therapeutic targets, such as ADAM-17, SARS-CoV ssRNA, DUSP1 and p38 MAPK (Gubernatorova et al., 2020). These data are consistent with the cytokine profiles observed in patients diagnosed with SARS, who, indeed, showed a marked elevation of T-helper lymphocyte type 1 (Th1) cytokine interferon- γ (IFN- γ), inflammatory cytokines (i.e., IL-1 β , IL-6 and IL-12) for at least two weeks after disease onset. Children, however, presented a much milder cytokine and chemokine storm. The high levels of IL-6 in the acute stage associated with lung lesions in SARS patients have been demonstrated to be activated by the viral nucleocapsid SARS-CoV N protein. Over induction of inflammatory cytokine and dysregulation of cytokine signaling have been observed in patients with SARS in comparison with other respiratory viruses, including respiratory syncytial virus (RSV), influenza A virus (FluAV), and human parainfluenza virus type 2 (hPIV2) (Okabayashi et al., 2006). SARS-CoV and RSV induced high levels of IL-6 and RANTES compared with FluAV and hPIV2. Changes in plasma Th cell cytokines, inflammatory cytokines, and chemokines in 20 patients diagnosed with SARS have been additionally reported. The elevation of Th1 cytokine IFN- γ , inflammatory cytokines IL-1, IL-6 and IL-12 and chemokines IL-8, MCP-1 and IP-10 has confirmed the activation of Th1 cell-mediated immunity and hyper-innate inflammatory response in SARS through the accumulation of monocytes/macrophages and neutrophils. Furthermore, a cytokine profiling has been also performed for 110 serum from healthy donors, patients with SARS, patients with severe SARS, and patients with SARS in convalescence. IL6 concentrations were significantly elevated in severe SARS patients, but the IL-6 concentrations were similar in convalescent patients and control subjects which suggested that IL6 is associated with SARS severity (Okabayashi et al., 2006). The N-protein of SARS-CoV have been shown to induce pulmonary inflammatory reaction and acute lung injury related to the increase and imbalance of pro-inflammatory and anti-inflammatory cytokines. Glucocorticoids could effectively alleviate the pulmonary inflammatory reaction induced by N-protein of SARS-CoV. SARS-CoV does not productively infect human macrophages (Mphi) or dendritic cells (DCs), however it modulates a massive release of IL-6 and IL-12 and compromises the endocytic capacity (e.g., antigen capture capture) of Mphi (Hao et al., 2005). Cytokine circulating level setting and evaluation of cytokine production have been largely studied as longevity markers. Accordingly, sequence variations in several cytokine genes, such as IFN- γ and IL-10 genes, have been demonstrated to be associated with successful ageing

and longevity (Caruso et al., 2005; Lio et al., 2004; Forte et al., 2009). On the other hand, individual changes in type and intensity of immune response affecting life span expectancy and health ageing seem to have a genetic component. A well-preserved immune function characterizing the successful ageing has been found in centenarians (Caruso et al., 2005; Lio et al., 2004; Forte et al., 2009) (Table 3). Recent evidence suggests that centenarians seem to be genetically equipped for overcome the major age-related diseases. Associations between both cytokine gene polymorphisms and longevity, and differential gender longevity in males and females, and reciprocally to age-related diseases have been demonstrated (Balistreri et al., 2012). Serum IL-6 has been proposed as a reliable marker for functional decline, as a predictor of morbidity and mortality in old age and increases in IL-6 have been associated with functional disability, cognitive decline, and stroke in older people (Cardoso et al., 2018). On the other hands, increase with age of IL-6 plasma levels appears to be unexpectedly present in both persons who enjoyed successful aging and those who suffered pathological aging (Franceschi et al., 2000). This increase continues with age, until the extreme limit of human life, and high levels of IL-6 are found in a high percentage of centenarians in good shape (Franceschi et al., 2000). The IL-6 production appears to be controlled at genetic level. A SNP in the promoter region (-174 G/C) seems to be associated with variations of IL-6 gene expression and serum levels, being homozygous GG and CC genotypes associated respectively with higher and lower levels of IL-6 serum levels (Singh et al., 2020). A recent meta-analysis confirms the association between the IL-6 polymorphism and the probability of achieving a very old age (>100 years) and the IL-6 -174 GG genotype appeared to be negatively associated with longevity and reduced the chance for male GG carriers achieving centenarian status (Di Bona et al., 2009). Thus, it may speculate that a genetically determined low IL-6 response to acute stressors, might at least partially account for the favorable outcome of COVID-19 in over 90 male patients. Other data obtained in Sicilian population confirm these associations and suggest that differences in the genetic regulation of immune inflammatory processes might explain the reason why some people but not others develop age-related diseases and why some develop a greater inflammatory response than others (Balistreri et al., 2012). This suggestion

Table 3
The polymorphic variants of proinflammatory and anti-inflammatory cytokines.

GENE	POLYMORPHISM	GENOTYPE	ASSOCIATION	REFERENCES
IL-6	rs1800795 G/C	GG	longevity	Di Bona et al. (2009)
IFN- γ	rs24030561 T/A	T/*	longevity	Lio et al. (2003)
TNF- α	rs1800629 G/A	G/*	longevity	Cardelli et al. (2008)
IL-10	rs1800872 C/A	C/*	longevity	Lio et al. (2003)
IL-10	rs1800871 C/T	C/* GCC/*		
IL-10	rs1800896 G/A	G/+		

The severe and fatal evolution of the Sars Cov2 infection is related to the extensive and intense production of proinflammatory cytokines, including IL-6 which has also taken on a leading role in therapeutic intervention. gene promoters of the cytokines examined create efficient transcriptional interaction sites. In this perspective, the 308A variants of TNF α or -174C of IL-6 and + 874 T of IFN- γ have been associated in the literature with a greater expression of these proinflammatory cytokines. Yet, in the gene promoter of IL-10, negative modulator of cell-mediated immunity and inflammatory response, SNPs are present in linkage disequilibrium: (-1082A / G, -819C / T and -592 C / T) which outline some haplotypes: GCC, ACC, ATA. GCC is associated with the higher production of IL-10, ATA with the lower expression of the cytokine. Individuality in the immune response could also be linked to these immunogenetic characteristics. The synthesis of IFN- γ is also conditioned by a linkage polymorphism with a microsatellite intronic allele CA (12 repeats). The most frequent "high producer" IFN- γ allele in long-lived is associated with better cell-mediated activity. More in general, in the centenarians a molecular profile characterized by "anti-inflammatory" alleles was observed, which suggests moderate management of inflammation resulting from SARS Cov2 infection.

seems to be suitable for some SNPs in IFN- γ and IL-10 genes. IFN- γ gene codifies for a cytokine involved in defense against viruses and intracellular pathogens, and in induction of immune mediated inflammatory responses. Its production is genetically regulated. A variable length CA repeat sequence in the first intron of IFN- γ gene has been described to be associated with high IFN- γ production (Lio et al., 2002b, 2002c; Lio et al., 2003). Furthermore, a SNP, T to A (+874 T/A), at 59 end of the CA repeat region has been described and T presence has been related to high producing microsatellite allele 2. This SNP coincides with a putative NF-kB binding site, which might have functional consequences for transcription of IFN- γ gene. Thus, this SNP might directly influence IFN- γ production levels associated with CA microsatellite marker (Lio et al., 2002a, 2002b, 2003). IL-10 gene codifies for IL-10 cytokine. IL-10 is produced by macrophages, T and B cells. It is one of the major immune-regulatory cytokines, usually considered to mediate a potent down-regulation of inflammatory responses (Lio et al., 2002b, 2002c, 2003). IL-10 production, independently on interaction with other cytokine gene products, is generally controlled by several polymorphic elements in the 5' flanking region of IL-10 gene. Multiple SNPs have been identified in human IL-10 5' flanking region and some (i.e. -592, -819, -1082) combine with microsatellite alleles to form haplotype associated with differential IL-10 production. These three SNPs in the IL-10 proximal gene region (considered potential targets for transcription regulating factors) might be involved in genetic control of IL-10 production, even if contrasting literature data have been reported. In particular, the homozygous -1082 GG genotype has been demonstrated to be associated with higher IL-10 production respect to G/A heterozygous and AA homozygous genotypes (Lio et al., 2002a, 2002b, 2003, 2004). Furthermore, this SNP appears to be functionally relevant. It has been shown that -1082 A carriers (low producers) likely develop a major number of chronic inflammatory diseases. Our results demonstrated an increase frequency of the -1082 G IL-10 allele in centenarian men (Lio et al., 2002b, 2002c, 2003, 2004). Such allele has been associated with significantly increased IL-10 production. On the other hand, our immune system has evolved to control pathogens, and pro-inflammatory responses are likely programmed by evolution to resist to fatal infections. Accordingly, low IL-10 production is correlated with increased resistance to pathogens. In older ages not evolutionally programmed, increased IL-10 levels might improve the control of inflammatory responses induced by chronic vessel damage and reduce the risk to atherogenic complications. These conditions might permit to achieve exceptional ages in an environmental with a reduced pathogen load. In an evolutionary perspective, it appears interesting that female Sicilian centenarians are characterized by an over-representation of +874 INF- γ allele. The INF- γ production is also influenced by hormonal control fundamentally mediated by 17b estradiol. Hormonal regulation of INF- γ has been suggested to regulate, in part, the ability of estrogens in modulating positively many types of immune responses and anti-viral immunity (Lio et al., 2002b, 2002c, 2003, 2004; Forte et al., 2009). The COVID-19 infection is associated with a robust IFN suppression with lymphopenia as part of the virally induced immunosuppression. Additionally, preliminary data reveal that disease severity in COVID-19 may be associated with low IFN- γ production from CD4+T-cells. Both IFN- β and IFN- γ inhibit the replication of the related SARS-CoV, but SARS-CoV virus N and proteins open reading frame (ORF) act as antagonists to the INF pathway by regulating IFN- β synthesis and signaling. In this scenario, a genetic setting associated with an increased IFN- γ production may help to evocate an efficient response to human Coronaviruses (Kopecky-Bromberg et al., 2007; McGonagle et al., 2020). All together data on genetic background of cytokine network in centenarians strongly emphasize that an optimal cytokine network genetic control might protect some subjects by detrimental effect of an excessive cytokine response. This would be the case of the cytokine storm associated with CoVID-19 (Fig. 2).

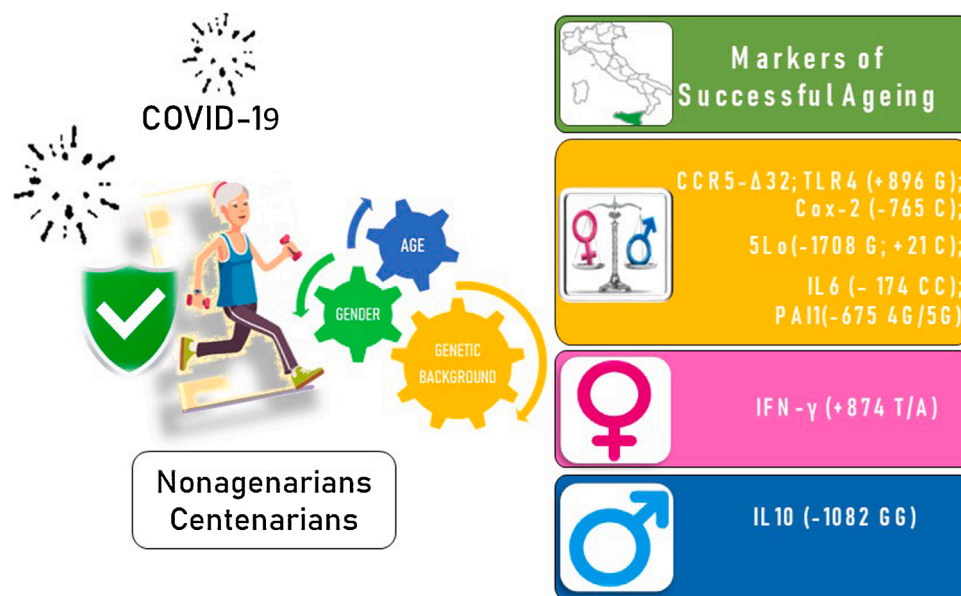


Fig. 2. COVID-19: What can we learn from studies of genetic background of long-lived subjects? The Figure shows some polymorphisms studied in nonagenarians/centenarians. SNPs of innate immunity and cytokine genes that play a key role in the regulation of inflammatory response and are associated to longevity, might be implied in the modulation of the age and gender dependent intensity of anti SARS-CoV2 immune-response.

5. SARS COV-2 infection. Epigenetics view from longevity studies

The ageing process and longevity are multi-factorial events. Genetic, epigenetic, stochastic, and environmental factors appear to have a crucial role in both the two processes. Epigenetics is associated with ageing, as shown in many studies (Moskalev et al., 2014; Park et al., 2012). Accordingly, it has been demonstrated that ageing is associated with a global loss of methylation state (Moskalev et al., 2014; Park et al., 2012). However, tissue dependent age-related hypermethylation of specific DNA regions have been also observed (Fuks et al., 2005; Portela and Esteller, 2010). These observations have led to address the research on epigenomics and its implication in ageing and longevity. Epigenomics is the systematic study of the global gene expression changes due to epigenetic mechanisms, but not to DNA base sequence variations. Epigenetic mechanisms consist in heritable modification that result in a selective gene expression or repression and consequently in phenotype changes (Wu and Morris, 2001). These changes include nucleosome positioning, post-translation histone modifications, action of small RNAs, DNA replication timing, heterochromatinization and DNA methylation (Moskalev et al., 2014; Park et al., 2012). This last consists in adding a methyl group (-CH₃) in the carbon 5 of cytosines, particularly in the CpG dinucleotide. This condition specifically concerns the CpG islands (CpGIs), located at the regulatory site of gene promoter regions. Methylation rate is associated with transcriptional regulation. Gene silencing is associated with increase of -CH₃ groups on DNA, and hypomethylation of CGIs is associated with an open chromatin state resulting in gene expression (Moskalev et al., 2014; Park et al., 2012). In the context of COVID-19, epigenetic modification involving crucial genes might play a crucial role. Precisely, it has been reported that the modulation of ACE2 gene expression depends on sirtuins (SIRT)-mediated control under hypoxia and increased IL-1 β levels (Clarke et al., 2014). Accordingly, ACE2 has been demonstrated to be up-regulated by IL-1 β treatment (Perkins et al., 2008). Early-stage clinical trials are currently in progress. They are, exactly, investigating the efficacy of recombinant ACE2 as a viable treatment for acute respiratory distress syndrome (ARDS) and other disease conditions associated with an imbalance of the RAS (Haschke et al., 2013). Regulation of ACE2 by IL-1 β may explain the protective increase in ACE2 levels reported in ARDS and may explain the coordinated changes in ACE2 and ACE

observed in several inflammatory conditions. In addition, IL-1 β treatments can alter the levels of SIRT1. In turn, SIRT1 regulates expression of diverse genes, such as ACE2 gene, by modulating transcription factors under altered redox states, resulting from conditions of low-oxygen and low-energy, such as after exercise (Zhang et al., 2010). Clarke and co-workers evidence that IL-1 β -induced ACE2 expression is associated with altered SIRT1, whose regulation by inflammatory conditions appears to be dependent upon the initial stimulus. SIRT1 is an NAD⁺-dependent class III histone deacetylase (HDAC), which attracts extensive research interests, because has been demonstrated to function as a longevity factor in mammals (Clarke et al., 2014; Hubbard and Sinclair, 2014). In addition to its crucial roles in the control of senescence, recent studies have found that SIRT1 exhibits pronounced anti-inflammatory properties via deacetylation of several inflammation-associated transcription factors (Clarke et al., 2014; Hubbard and Sinclair, 2014). Consequently, SIRT1 is considered as a novel target for the negative regulation of inflammation, and several SIRT1 activators have shown positive effects in animal models of inflammatory disorders. However, just like the dual effects associated with other post-translational modifications (PTMs), such as phosphorylation, polyubiquitination and SUMOylation, SIRT1-mediated deacetylation might not always be associated with negative effects on inflammatory response (Liu et al., 2016). It has been also reported that acetylation of p65 is required for the full activity of NF- κ B, associated with increased expression of pro-inflammatory genes (Xie et al., 2013). On the contrary, acetylation of mitogen-activated protein kinase phosphatase-1 (MKP-1) enhances the interaction of MKP-1 with p38, which is associated with decreased phosphorylation of p38 and the suppressed inflammatory response (Chi and Flavell, 2008). Thus, acetylation modifications might have both positive and negative effects on inflammation-related proteins. Likewise, it is possible that SIRT1 might have both beneficial or detrimental effects under certain inflammatory conditions. In a recent paper, Huang and coworkers (Huang et al., 2017) have demonstrated by using an animal model that selective inhibition of SIRT1 might alleviate acute lung injury, including leukocytes infiltration, hemorrhage, bronchial wall thickening and alveolar edema, induced by endotoxemia. SIRT1 inhibition has been observed to suppress LPS-induced elevation of TNF- α and IL-6 in plasma, attenuate LPS-induced histological abnormalities in lung tissue, and suppress up-regulation of tissue factor and plasminogen activator inhibitor-1 that might contribute to abnormal activation of coagulation

and the exacerbated tissue injury (Levi and van der Poll, 2017). Since cytokine storm and coagulation disorders are two of major detrimental effects of SARS CoV2, lung tissues infection studies on SIRT-1 pharmacological modulation might be useful to develop therapeutic strategies against COVID-19.

6. Genetic determinants of coagulation in longevity. Perspective for COVID-19 therapy

In patients who develop sepsis caused by various infectious agents, the onset of coagulopathy is one of the key and persistent features, associated with poor outcomes (Arachchillage and Laffan, 2020). Concerning COVID-19 infection, this is an area not been well studied at this time. The hemostatic system alterations include changes in the activated partial thromboplastin time (aPTT), in the international normalized ratio (INR) of the prothrombin time, increased D-dimer and fibrin degradation products (FDP). Patterns of disseminated intravascular coagulation (DIC) have been reported in deceased patients with COVID-19 infection. In the largest analysis of clinical cases published, an extremely significant increase of D-dimer has been noted in about 60 % of patients with a severe illness (older individuals and those who have one or more co-morbidities) and development of DIC characterizes >70 % of patients who did not survive the infection (Guan et al., 2020; Ranucci et al., 2020). Based on this study and the experience from published literature on septic coagulopathy, monitoring PT, D-dimer, platelet count and fibrinogen are considered helpful in determining prognosis in COVID-19 patients (Barrett et al., 2020). On the other hand, SARS CoV2 infects endothelial cells (EC), that, in old individuals, result commonly affected by different baseline damages (Jia et al., 2019). Aged EC usually become flatter and enlarged with an increasingly polypoid nucleus. These changes are accompanied by modulation in cytoskeleton integrity, angiogenesis, proliferation, and cell migration (Rossman et al., 2017). For instance, senescent EC show attenuated endothelial nitric oxide (NO) production, increased endothelin-1 (ET-1) release, elevated inflammation, and cell apoptosis (Balistreri, 2016, 2017; Buffa et al., 2019). Thus, EC senescence induces vascular structural, and functional changes enhance thrombosis, and inflammation with impairment of vessel tone, angiogenesis, and vascular integrity, all of which nowadays might contribute to development and progression of a severe COVID-19 (Balistreri, 2016, 2017; Buffa et al., 2019; Rossman et al., 2017). Molecular proteins and signaling pathways, including Sirtuins and Fibroblast growth factor 21 (FGF21), contribute to these pathophysiological changes. Further, accumulation of genetic damage and epigenetic alterations impact the normal gene expression and activity, resulting in cellular senescence and vascular dysfunction (Wang et al., 2016). In this context, a remarkable role is played by Sirtuins. Pharmacological or endogen activation of SIRT1 modulates RAS axis, down-regulating AT1R expression via ACE2 upregulation and activation of AT2R, preventing inflammation related vascular damages (Magrone et al., 2020). In a recent study, Gaul and coworkers (Gaul et al., 2018) have reported that SIRT3 also influences arterial thrombosis in a neutrophil-dependent mechanism. Using a laser-induced carotid thrombosis model combined with LPS challenge, authors observed that SIRT3 genetic ablation causes a significant acceleration resulted in enhanced clot formation and increased clot firmness. SIRT3 is a mitochondrial isoform that catalyzes protein deacetylation using nicotinamide adenine dinucleotide (NAD) as a co-substrate. In humans, genetic polymorphism increasing *SIRT3* gene expression has been associated with an increased lifespan, whereas mutations that reduce SIRT3 activity have been associated with MI and metabolic syndrome (Albani et al., 2014) (Table 4). On the other hand, studies on centenarians have demonstrated that in extreme old age may be observed an increased coagulative response, accompanied by signs of enhanced formation of fibrin and secondary hyperfibrinolysis. It is of interest that centenarians have a significantly higher frequency than young individuals of the high risk 4 G allele of the *PAI-1-675* (4 G/5 G) polymorphism, mutant factor V

Table 4

The coagulation paradox in centenarians. SNPs and epigenetic interplay.

GENE	POLYMORPHISM	GENOTYPE	ASSOCIATION	REFERENCES
SIRT3	rs 4,980,329 G/A	A/*	longevity	Albani et al. (2014)
SIRT3	rs 11,555,236 G/T	T/*	longevity	Albani et al. (2014)
PAI-1	rs2020918 4 G/5 G	4 G/4 G	↑SIRT3	
Factor V	rs6025 G/A	A/*	longevity	Mari et al. (2008)
FII	rs 1,799,963 G/A	A/*		

Since some interstitial pneumonia from SARS Cov2 have an inauspicious outcome, with ARDS and CID, it could be significant to analyze the genetic background relating to coagulation factors to assess their impact on the evolution of the disease. Paradoxically, alleles associated with increased procoagulant activity appear more frequent in long-lived: i.e. 1691A of Factor V (G1691A), 20210A (G20210A) of Factor II (G2010A) and 4 G of PAI-1 (4 G / 5 G). The SIRT3 epigenetic modulator, considered not by chance a longevity marker for negative control of inflammation and coagulation, has SNP variants associated with increased expression, which are more frequent in centenarians. Probably a complex mosaic of gene and epigenetic interactions is the basis of the functional model of immune response.

(Arg506Gln) and prothrombin gene *G20210A* mutation (Mari et al., 2008) (Table 4). This apparently striking paradox accounts for the complex genetic and epigenetic network that influence the life span expectancy and the response to environmental challenges. SARS CoV2 infection affects at different levels natural and acquired defense systems (innate immunity, stress, and inflammation). Thus, components of favorable architecture of defense system network, that could allow to reach the extreme longevity might be considered promising target for COVID-19 therapy.

7. Discussion and conclusions

As amply stressed in this report, three factors i) the role of genetic background, ii) age and iii) and gender of the host impact the clinical outcome of COVID-19 infection, largely variable, ranging from asymptomatic to lethal. Here, we have largely stressed these factors, by assuming the perspective acquired by studies on genetic and epigenetic factors influencing the so called “longevity trait.” We have especially described the role of genetic variants in *ACE2*, *immune innate*, *coagulation system* genes, and the effects of diverse epigenetics factors modulating their expression, such as those related to SIRT-1 action, that have reported to affect susceptibility and/or protection against SARS COV2.

In the complex, the three factors can help us to explain how many COVID-19 patients become severely sick and may die, but others recover from illness and complications or have no signs or symptoms of disease as recently reported for a group of Italian male centenarians (Marcon et al., 2020). In 1955, René Dubos (Dubos, 1955) attributed this feature to pathogen itself, as stressed in “the gem theory of disease”. However, the group of Casadevall (Casadevall and Pirofski, 2018) has largely studied this aspect, by analyzing 11 features (i.e., microbiome, inoculum, sex, temperature, environment, age, chance, history, immunity, nutrition, and genetics). Sex, age, immunity, and genetics of the host have been suggested to be extremely relevant, and their combination has been proposed as a key factor for identifying “the signatures of susceptibility and clinical outcomes”. Recently, Casanova and Abel (2018), have evidenced that the variability of clinical outcomes of an infection among people is significantly established by the germline genetics of the human host. Obviously, host germline genome can impact innate and adaptive responses and set the outcomes after the contact of a microbe with the host. Based on these concepts, they have divided human genes into four categories according to their level of redundancy for protective immunity to infection in natural conditions. First category is given by

genes with low redundancy, defined by the lack of the protein encoded that confers high vulnerability to a broad range of microbes in most, if not all patients, by causing the disruption of a key immunological component; the second includes genes defined with high redundant, when lack of the protein encoded gives vulnerability to a narrow range of microbes, sometimes a single pathogen, in a certain number of patients; the third given by if gene completely redundant when the deficit of protein encoded is apparently neutral, and may lead to a no valuable predisposition to infection in everybody; the fourth, finally, is represented by the gene with beneficial redundancy, if the lack of a protein may, paradoxically, be advantageous to the host, conferring resistance to one or more infections, such as the HIV protection in absent of CCR5 in carriers with CCR5Δ32 variant (Balistreri et al., 2007), or that against the pathogen of Boutonneuse fever in carriers +869 G TLR4 variant (Balistreri et al., 2005). Similarly, we speculate that some genetic variants in ACE2, able to modulate function and expression, might confer COVID-19 resistance or reduce susceptibility to the most severe disease complications in infected individuals.

Very old people, including nonagenarians and centenarians, show a gathering of genetic variants in immune/inflammatory genes, mostly with anti-inflammatory biological effects, that confer them an optimal performance of immune system and might be included in the group of genes with beneficial redundancy (Balistreri et al., 2012). In addition, the variants observed in long-lived people benefit from the effects of antagonist pleiotropy, that is consented as part of multi-controlled selection processes, enabling the persistence of genetic variations, including the immune/inflammatory genetic profiles peculiar in genetic background of long-lived people as evidenced in our and other studies (Balistreri et al., 2012; Mérot et al., 2020). The aspects above reviewed lead us to suggest that the study of long-lived people that survived COVID, might facilitate identifying of the genetic basis of resistance to SARS-CoV-2 and provide a pharmacological target for preventing or reducing viral infection in other individuals. In addition, investigations in female nonagenarians/centenarians might be useful for a differential treatment between the sexes. However, in the studies on long-lived people is to consider that the genetics of longevity is context depending. Consequently, the associations of protective and risk variants may change by studying different birth cohorts, populations with diverse ethnicity and ancestry, and age because of pleiotropic antagonism. This suggests that is possible to detect “relative associations” (not absolute). Thus, the aim of the suggested studies is to identify “relative variants” that are the result of combinations of interactions of genome with environmental and that might provide advances not only for COVID-19, but also for other aggressive infection. In this framework, investigations on deeply phenotyped very old subjects (i.e. reaching the limit of 120 years) recovered from illness and complications of COVID-19, or having no signs or symptoms of disease, from a precise area and population, and fully analyzed using multi-omics technologies, should be encouraged. This approach would be accompanied by the multicentric large worldwide projects that reduce all these effective variables. The main limitation involves statistical difficulties in identifying true positive associations and at the same time reducing the generalizability of the results. Finally, since longevity is not completely characterized by the absence of risk variants, but rather by the absence or delay of pathologies, the model on long-lived people is useful to add a biological interpretation of the variants called “risk alleles” for infection and for the identification of protective genome/environmental interactions. The reasons of long-lived people to carry these variants are diverse, including 1) the environment, where they live, can neutralize the risk; or 2) these risk alleles interact with other variants that change the association. In both cases, the information that this model can impact, can be used for human genetics associated with infection, if we theoretically place the 2 phenotypes (longevity and infections) to two extremes of the same phenotypic spectrum. For concluding, the study on COVID-19 pandemic should make us consider an alternative approach to studying infectious diseases, for diverse reasons: a) the enormous

inter-individual clinical variability in response to its exposure, ranging from resistance to death, and everything in between; b) comparable variability for all human-tropic microbes, such as viruses, bacteria, fungi, or parasites. The proportion of life-threatening cases varies among microbes, from less than one in a million to greater than one in ten. This clinical variability during primary infection remarks the fundamental “infection enigma” (Dubos, 1955), and to lead to hypothesize that the clinical manifestations of human infections, including SARS-CoV-2, can be regulated by human genetics, at least in outliers resistant to infection or unusually prone to severe disease.

Authors' contributions

DL and CRB conceived and designed the study. CRB, LS, and DL wrote the manuscript. CRB and DL reviewed it. LS and RG prepared figures and tables. CRB gave the final approval of the version to be published. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors have no conflict of interest to disclosure.

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