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Review

Triple jeopardy in ageing: COVID-19, co-morbidities and inflamm-ageing

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ABSTRACT

Covid-19 endangers lives, has disrupted normal life, changed the way medicine is practised and is likely to alter our world for the foreseeable future. Almost two years on since the presumptive first diagnosis of COVID-19 in China, more than two hundred and fifty million cases have been confirmed and more than five million people have died globally, with the figures rising daily. One of the most striking aspects of COVID-19 illness is the marked difference in individuals' experiences of the disease. Some, most often younger groups, are asymptomatic, whereas others become severely ill with acute respiratory distress syndrome (ARDS), pneumonia or proceed to fatal organ disease. The highest death rates are in the older and oldest age groups and in people with co-morbidities such as diabetes, heart disease and obesity. Three major questions seem important to consider. What do we understand about changes in the immune system that might contribute to the older person's risk of developing severe COVID-19? What factors contribute to the higher morbidity and mortality in older people with COVID-19? How could immunocompetence in the older and the frailest individuals and populations be supported and enhanced to give protection from serious COVID-19 illness?

1. COVID-19 highjacks and controls cells

Early in infection, the SARS-CoV-2 virus targets the nasal and bronchial epithelium and cells of the lung. It uses its viral structural spike protein (S) to bind to the angiotensin-converting enzyme 2 (ACE2) receptor on the host cell surface, where the transmembrane serine protease (TMPRSS2) cleaves ACE2 and activates SARS-CoV-2-S protein, allowing coronavirus to enter the host cells (Hoffman et al., 2020) (Fig. 1A). Neuropilin-1(NRP1), recently identified as a host factor, potentiates the SARS-CoV-2 infectivity (Daly et al., 2020).

COVID-19 uses the internal machinery of the host cell to replicate so that huge numbers of new SARS-CoV-2 viruses emerge into the blood stream. COVID-19 then further replicates itself unrecognised within the host cell by blocking the cell's normal defence molecule – interferon gamma (IFN), that would normally be the primary counter-acting cytokine to initiate an effective immune response, halting the viral invasion.

Similar to infection with other respiratory viruses such as influenza, lymphopenia often develops with COVID-19 illness (Qin et al., 2020; Huang et al., 2020a), which likely contributes to the failure to limit viral replication so that widespread viral dissemination progresses to severe illness (Huang and Pranata, 2020; Tan et al., 2020a). Although T cell depletion in the blood is not well understood, excessive IL-6 production can block lymphopoiesis (Maeda et al., 2005). The SARS-CoV-2 viral-induced inflammatory responses can lead to spleen and lymph node damage inducing secondary lymphopoiesis, and as lymphocytes themselves express ACE2 receptor they may therefore be a direct target of SARS-CoV-2 infection (Tan et al., 2020a; Feng et al., 2020).

In severe COVID-19, fulminant activation of the coagulation cascade, with consumption of clotting factors, can occur with symptoms and findings consistent with disseminated intravascular coagulation (DIC) (Lodigiani et al., 2020; Ackermann et al., 2020). Microthrombi occur in the lungs and thrombotic complications develop in arteries and veins causing deep venous thrombosis, pulmonary embolism, stroke and myocardial infarction.

In later stages, as COVID-19 viral replication increases, the epithelial-endothelial barrier becomes damaged and pulmonary endothelial capillary cells become infected, increasing the inflammatory lung damage (Varga et al., 2020; Channappanar and Perlman, 2017). The evolving inflammation cascade of cytokines, chemokines and necrotic cell debris, causes diffuse thickening of alveolar walls and interstitial mononuclear inflammatory infiltrates (Fig. 3F). As oedema develops,

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ground glass opacities present on X-ray computerised tomographic (CT) imaging, visually represent the dysfunctional alveolar-capillary oxygen transmission and impaired oxygen capacity that presents clinically, with silent hypo-oxygenation and critical illness in COVID-19 patients.

The COVID-19 viral sepsis with life-threatening organ dysfunction is caused by a severely dysregulated host response to infection stimulating a systemic cytokine storm which becomes uncontrolled, and further contributes to tissue damage, multi-organ failure and death.

2. Is the immune system in older people fit for purpose in its response to COVID-19?

2.1. Reduced early T cell progenitors emerge from bone marrow

As age increases, the bone marrow (BM) has a reduced ability to produce hematopoietic stem cells for self-renewal (Kovtonyuk et al., 2016; Latchney and Calvi, 2017) (Fig. 2). There is a skewing towards myeloid cell production with fewer lymphocytes entering the circulation. In BM ablation treatment of haematological cancers, whilst progenitor B cell numbers recover, clinical teams have demonstrated markedly reduced capacity of bone marrow and lymphatic system in older recipients to re-populate their marrow with new naïve T cells (Mackall et al., 1995). We have observed a decreasing ability to restore T cell populations in our patient-recipients of autologous peripheral blood stem cell transplants (ASCT) as treatment for haematological malignancies, with older patients (>55 years) continuing to have CD4+ T cell lymphopenias 4–5 years after transplant (Alexander, 2021).

The reduced capacity of the BM to renew T cell progenitors, puts older people at immune disadvantage when faced with a significant viral infection such as SARS-CoV-2.

2.2. Involution of the thymus produces fewer naïve T cells

Human naive T cells are largely produced early in life when the infant thymus is large and functional, whereas with age-related involution, the thymus shows decreased cellularity, with increased adipose tissue (Palmer, 2013; Sun et al., 2012). Age-related changes are associated with reduced numbers of CD4+ naïve cells (Wang et al., 2021a; Strindhall et al., 2013; Rea et al., 1996a) (Fig. 2). Naïve T cells, newly emergent T cells from the thymus, with predefined antigen specificity following rearrangement of T cell receptor genes, circulate between blood and lymphoid tissue. Each CD4+ T cell has a different specificity with potential to respond to novel antigens, such as the SARS-CoV-2 virus. Age-related lower production and response to decreased IFN characterise the impaired immune response to new infections in older people (Molony et al., 2017; Haynes and Eaton, 2005; Rea et al., 1996b).

Without adequate numbers of naïve CD4+ T cells to respond to the unfamiliar SARS-CoV-2 virus, the immune response in older people, is less able to respond quickly and effectively and immunity is impaired.

2.3. Tissue resident macrophages (T_{RM}s), T-cell and B cell response in the lung in COVID-19

Tissue Resident Macrophages (T_{RM}s), if present in the lung tissue, can 'kick start' a prompt, effective IFN-guided immune response in people previously exposed to COVID-19 or related coronavirus (Grau-Expósito et al., 2021). However, T_{RM}s may less likely to be present in elderly people, self-isolating during the COVID-19 pandemic, to help generate an efficient immune response. Furthermore, the decreased numbers of CD4+ naïve cells, less effective T helper and B and cell interactions, reduced IFN signalling, contribute to the well-described impaired response after vaccination (Stebegg et al., 2020; Agrawal, 2013;

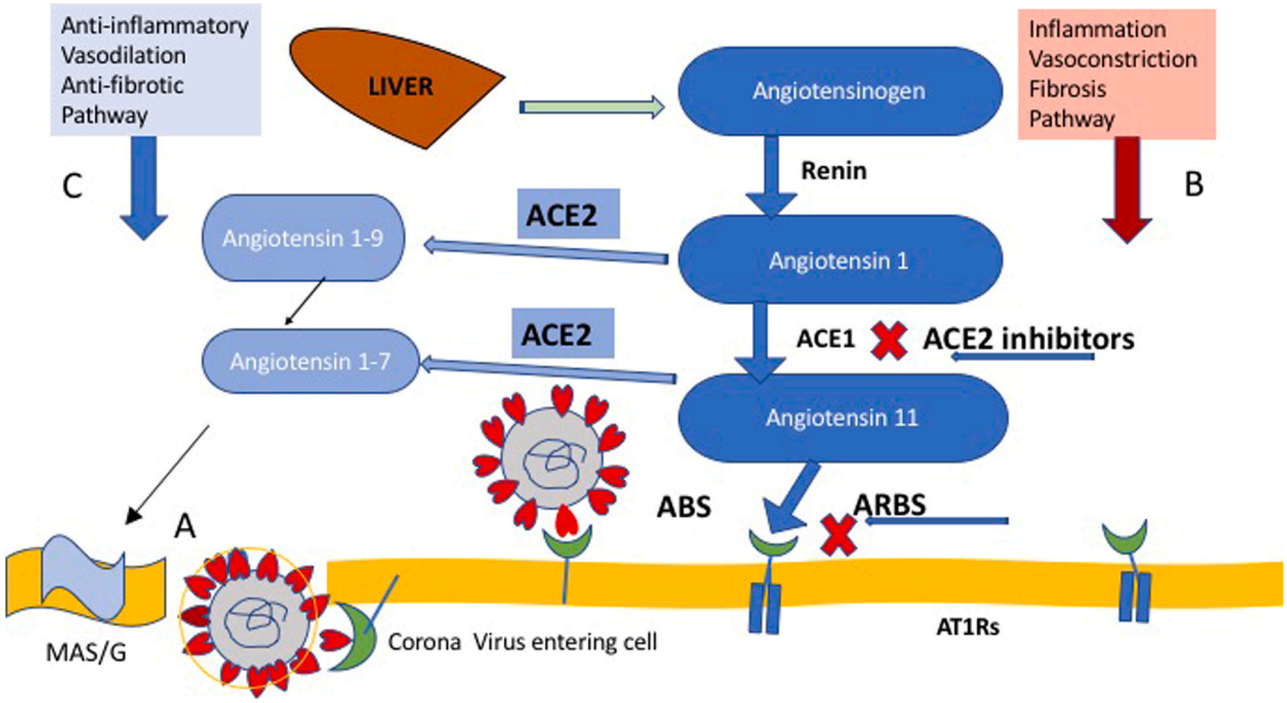

Fig. 1. ACE pathway and role of ACE2 in the pathogenesis of COVID-19 and the inflammatory Response. The lung loses ACE2-mediated protection following endocytosis of the enzyme with SARS-CoV-2 virus, as it enters cells in the lung and other organs [A]. The angiotensin-converting enzyme ACE enzyme cleaves Angiotensin I (Ang 1), generating Angiotensin 11 (Ang 11), which acts though the angiotensin 11 receptor (AT1R), to increase vasoconstriction, increase blood pressure and promote inflammation [B]. In the counter-regulatory pathway, ACE2, hydrolyses Ang 11 into heptapeptide angiotensin Ang (1–7), that acts through the ACE2/Ang1–7/MAS/G receptor pathway to downgrade the constrictive proliferative effect of Ang 11, and induce vasodilation, and reduce inflammation and fibrosis [C]. The ACE2 gene influences the renin angiotensin system (RAS) function by modulating blood pressure, sodium and fluid balance and may thereby be important in COVID-19 patients with cardiovascular and renal disease. ACE2, Angiotensin converting enzyme 2; AT1R, Angiotensin 1 Receptor; ACEi, Angiotensin converting enzyme inhibitors; ARBs, Angiotensin converting enzyme receptor blockers; MAS/G receptor, Mas-related g protein-coupled receptor.

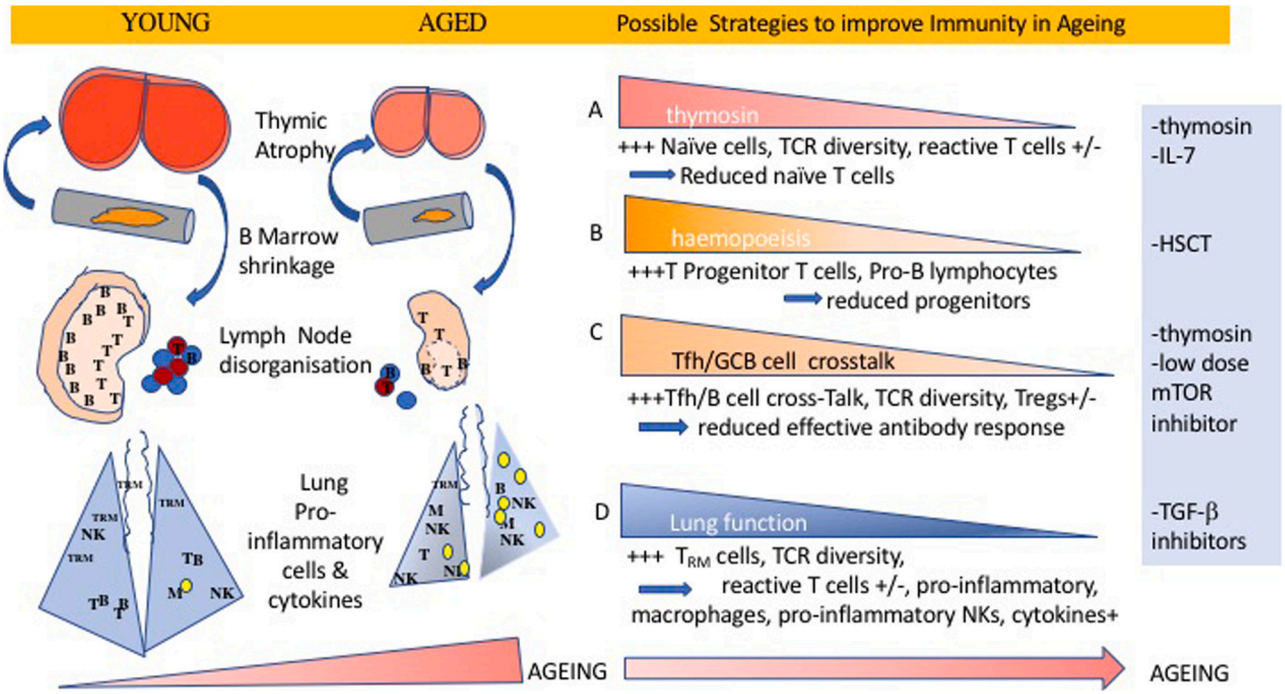

Fig. 2. Graphic of immune changes in ageing. A. The thymus atrophies and gets much smaller with age. B. The bone marrow (BM) area producing haematopoietic stem cells reduces with age. A&B Progenitor T cells and pro-B lymphocytes produced in the BM migrate to thymus and complete antigen-independent maturation into functional T cells, such as naïve T cells, and B cells. Thymic involution with ageing, reduces the output of naïve T cells. C. Reduced naïve CD4+ T cells, reduced T cell receptor (TCR) diversity, and disorganisation of lymph nodes with increasing age, results in less effective T follicular helper (TFh)/B cell interaction in germinal centres in peripheral lymph nodes. D. Less effective Tfh/B cell adaptive and specific antibody production in response to SARS-COV-2 virus, results in delayed containment and resolution of SARS-CoV-2 infection in the lungs in older people, often damaged by disease and with reduced respiratory function; therefore, there is increased potential for uncontrolled infection, increased tissue damage, development of cytokine storm and progression to multi-organ failure.

Agrawal et al., 2017) (Fig. 3).

The decreased numbers of CD4+ naïve cells, less effective T helper and B cell interactions, reduced IFN signalling due to impaired dendritic cell (DC) activation, and likely absence of T_{RM} cells, together contribute to a sluggish immune response in the lung in older people during COVID-19 illness, that is critical for effective recovery.

2.4. *Is the innate immune system out of control in COVID-19?*

Natural killer cells (NKs) and macrophages are the main innate leucocyte subsets that aim to stop the spread of the SARS-CoV-2 virus when inhaled into the lungs, from air droplets and aerosols of a COVID-19 carrier. T_{RM}s if present in lung tissue, sound the alarm, and macrophage and NKs recognise, destroy and engulf the SARS-CoV-2 virus by releasing damaging cytotoxic molecules, that stimulate the inflammasome and trigger pro-inflammatory cytokines. NKs and macrophages to track to the infected lung tissue, guided by chemokines, CCL3, CXCL3 and granulocyte macrophage-cell secreting factor (GM-CSF), secreted by type 11 alveolar cells (Fig. 3C–E).

The active bi-directional crosstalk and interaction between NK and DCs involving the secretion of cytokines (Jost and Altfeld, 2013; Ferlazzo and Moretta, 2014), is regulated by monocytes/neutrophils in a "menage a trois", so that a controlled and modulated production of IFN-γ by NK cells occurs for effective viral control (Wałajtys-Rode and Dzik, 2017). In serious COVID-19 illness, authors have reported fewer NK cells, some displaying an exhausted phenotype (Giamarellos-Bourboulis et al., 2020a; Kuri-Cervantes et al., 2020; Maucourant. et al., 2020), with NK numbers and cytotoxity improving with recovery (Rodriguez et al., 2020). Lower NK numbers may occur because NKs traffic to, and remain in the lungs, contributing further to the local milieu of inflammation injury (Liao et al., 2020; Zhou et al., 2020c). The lower numbers of dendritic cells (DCs) in older age, reduces capacity to produce IFN-γ that is essential to control Phase 1 of the inflammatory response to COVID-19 and stop the damaging SARS-CoV-2 virus replication early in the illness.

In older, healthy age-groups, there is a well-described age-related increase in CD3− CD56+ NK cells and NK-related subsets (Hazeldine and Lord, 2013; Yan et al., 2010; Le Garff-Tavernier et al., 2010; McNerlan et al., 1998). NK cells can produce both pro-inflammatory and anti-inflammatory cytokines, demonstrating that counterbalancing cytokine feedback loops are important during controlled innate immune responsiveness, homoeostasis and repair (Vivier and Ugolini, 2009; Rea et al., 2013) (Fig. 4). The age-related increase in NK and NKT-related cells likely contributes to the pro-inflammatory hyperinflammation and cellular damage seen in older individuals, in early COVID-19 illness.

An important aspect of NK function is the NK, Killer Immunoglobulin-like Receptors (KIRs) that control NK functions and can be classified into A and B haplotypes; A has an inhibitory role, compared to the activating role of B, which produces pro-inflammatory cytokines (Cisneros et al., 2020; Pegram et al., 2011) (Fig. 5). A balance between activating KIR A haplogroup and inhibiting KIR B group KIR genes ensures effective and timely immune surveillance by NK cells; when unregulated, their unbalanced activity contributes to uncontrolled inflammation (Lam and Lanier, 2017; Schmidt et al., 2016). In examining NK cell diversity, Horowitz et al. (2013), suggested that whereas genetics primarily determined inhibitory KIR B receptor expression, pro-inflammatory activating KIR A receptors were likely controlled by environmental factors. Could KIR haplotype A play a role in the social determinants of health such as smoking, obesity or poverty and predict a more activating damaging pro-inflammatory NK response to SARS-COV-2 infection? Furthermore, A and B KIR haplotypes demonstrate different frequencies across different populations, ethnicities and geographical locations, that could contribute to differences in how COVID-19 presents clinically, and with different patient outcomes (Yao et al., 2019; Norman et al., 2001; Guinan et al., 2010).

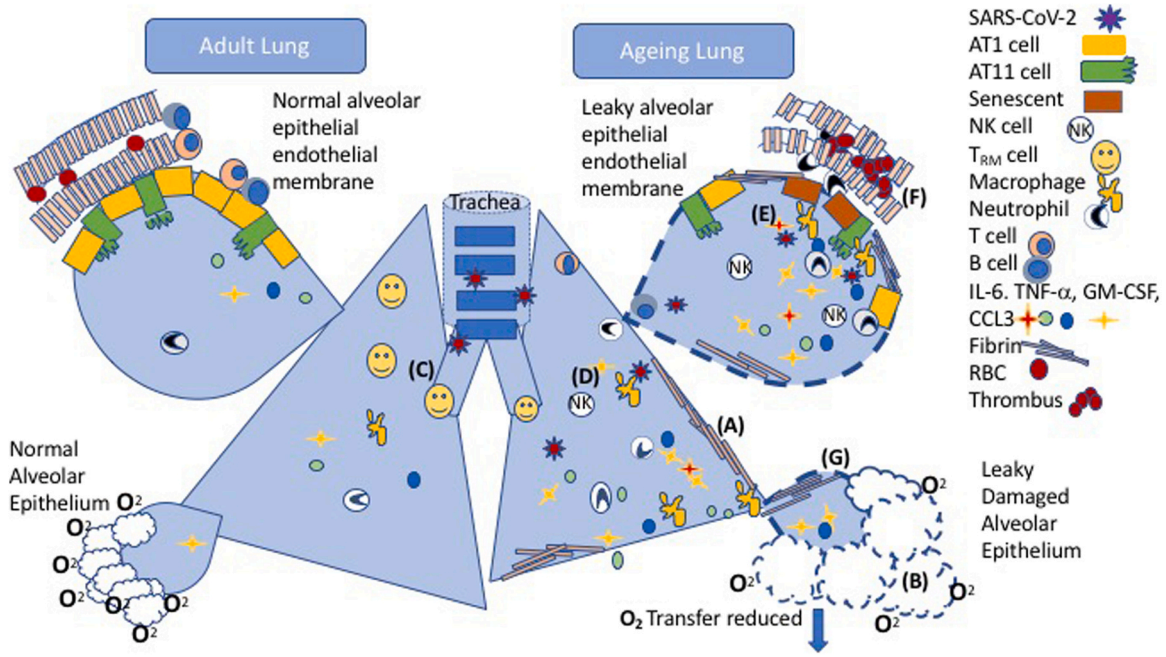

Fig. 3. SARS-CoV-2 virus-induced Inflammatory response in the Lung, is accentuated in Ageing. (A) In elderly individuals reduced lung elasticity and respiratory volume, increased fibrosis and inflammation from smoking, environmental toxin exposure, multiple disease pathologies and poorer respiratory function, compromise oxygen and blood gas exchange. (B) Alveolar epithelial cells AT1s, responsible for the integrity of the epithelial-endothelial barrier, are less elastic, the alveolar sacs become baggy, and gas exchange is reduced. (C) T_{RM}s holding memory from a SARS-CoV-2 or related-coronavirus infection, can 'kick start' immune response to new SARS-CoV-2 infections, but are unlikely to be present in older people who have spent months isolating during COVID-19 pandemic times. (D) Following SARS-COV-2 infection, NKs and macrophages go to the infected lung tissue, guided by chemokines, CCL3, CXCL3 and GM-CSF, secreted by type 11 alveolar cells (ATII). (E) Macrophages and NK cells recognise, engulf and destroy SARS-CoV-2 virus, and continue to release cytotoxic and cytokine molecules, in an ongoing, continuous cycle of inflammation. (F) In fulminant COVID-19 infection, more common in elderly patients, the epithelial-endothelial barrier becomes damaged and leaky, pulmonary epithelial cells become infected, interstitial oedema develops, and platelet-fibrin microthrombi form in capillaries, with risk of widespread venous and arterial thrombosis. (G) The evolving inflammation cascade causes diffuse thickening and fibrosis of alveolar walls with reduced oxygen diffusion and critical hypo-oxygenation, and multi-organ failure in ill COVID-19 patients. T_{RM}s, Tissue Resident Macrophages, NKs, natural killer cells, GM-CSF, granulocyte macrophage-cell secreting factor, AT1, type 1 alveolar cells, AT11, type 11 alveolar cells.

SARS-CoV-2, NK-driven viral destruction has the potential to cause severe self-damage, if phase 1 of the inflammatory response is ineffectively shut down, because of reduced IFN production in older age (Masselli et al., 2020; Jose and Manuel, 2020).

2.5. *Adaptive immunity in ageing and in COVID-19 illness*

Adaptive immunity relies on effective transfer of information between T and B cells, so that high quality specific antibodies which recognise surface antigens on the SARS-CoV-2 virus, can neutralise virus-infected cells. Differing subsets of CD4+ T cells, such as CD4 Tregs have a role in helping to damp down and control the NK and CD8+ T effector cells' potentially damaging and exuberant cytotoxic response to SARS-COV-2 virus (Okeke and Uzonna, 2019).

With increasing age, there is a gradual deterioration in the immune system that reduces an effective response to infections and vaccination and has been termed immunosenscence (Franceschi et al., 2000; Cunha et al., 2020; Pietrobon et al., 2020). The age-related changes in the T cell landscape show reduced T cell receptor (TCR) repertoire diversity, increased memory and self-reactive T cells and an accumulation of polyclonal regulatory T (Treg) cells that are associated with an increased background of inflammation called inflamm-geing (Franceschi et al., 2000, 2007; Franceschi and Campisi, 2014).

In age-related investigations in peripheral blood mononuclear cells, derived from healthy donors in a wide range of age-groups, the normal range of changes in the immune system with ageing have been characterised (Hirokawa et al., 2013; Wikby et al., 2008, 2002; Rea et al., 1999; McNerlan et al., 1999). Fluorescence-activated cell sorting and transcriptome sequencing show that lymphopenia occurs quite frequently, with CD4+ naïve T cells decreasing with age (Moro-Garcia et al., 2013; Derhovanessian et al., 2013; Rea et al., 1996), whereas antigen-experienced memory T cells increase with loss of co-stimulation factors CD27+ and CD28+ (Vescovini et al., 2014) (Fig. 6). The loss of CD28+ T cells is more pronounced in cytomegalovirus (CMV) seropositive donors, has been used as a marker of immunosenescence in older populations and together with an inverted CD4/CD8 ratio was identified as a biomarker of frailty and mortality in the OCTO immune study (Pawelec, 2012; Adriaensen et al., 2015; Wikby et al., 1998), though has not replicated in other older cohorts (Li et al., 2019; Rea et al., 2010).

Lymphopenia is a common feature in COVID-19 illness (Huang et al., 2020b), with markedly lower CD4+ and CD8+ T cell counts in patients in Intensive Care Units (ICU) and an age-dependent reduction of T cells in patients ≥ 60 years old (Diao et al., 2020). Reduced numbers of CD4+ T cells, CD8+ T cells, B cells and NK cells, irrespective of age have been consistently reported (Lucas et al., 2020; Braun et al., 2020; Grifoni et al., 2020), and would seriously compromise an integrated, effective immune response in the older person presenting with COVID-19 infection (Li et al., 2019; Lin et al., 2016; Rea et al., 1996). In comparing immune differences in COVID-19 patients and healthy individuals, using a systems biology approach, Arunachalam et al. (2020) demonstrated a reduced frequency of plasmacytoid dendritic cells (pDCs), reduced relative frequency of HLA-DR activation and pro-inflammatory cytokines by myeloid cells, together with impaired mTOR-signalling and IFN-α production. De Biasi et al. (2020), demonstrated a severely impaired immune system in COVID-19 patients, with reduced absolute numbers of CD4+ and CD8+ T lymphocytes showing activation or exhaustion/senescence markers, and elevation of pro- and anti-inflammatory cytokines-TNF, IFN-γ, IL-2 and IL-17. Sadeghi et al.

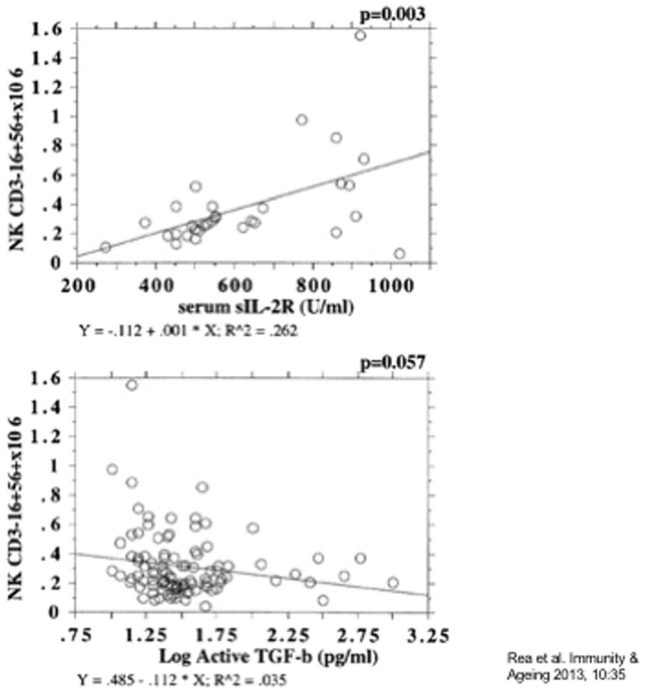

Fig. 4. Regression plots showing association for NK counts and pro-inflammatory and anti-inflammatory cytokines, sIL-2R and TGF-β, in Octo/nonagenarians from BELFAST study. (A) Regression plot showing association between NK count and serum IL-2R (A), with increases in NK cell number associated with increases in serum IL-2R, linked with increased inflammation. $r^2 = 0.262$, $p = 0.003$. (B) Regression plots showing association between NK count and log Active TGF-β, showing a negative association between NK count and the anti-inflammatory cytokine TGF-β, linked with resolving inflammation. $r^2 = 0.035$, $p = 0.057$. NKs, natural killer cells, BELFAST, Belfast Elderly Longitudinal Free-living Ageing Study.

(2021), similarly demonstrated elevated IL-17 and TH 17 cell numbers in ICU-SARS-CoV-2-patients.

Community-living older people also show quantitative and qualitative changes in the B lymphocyte pool (Blanco et al., 2018; Dunn-Walters, 2010; Frasca et al., 2011). B cells secrete TNF-α that further inhibits survival of B-cell precursors (Ratliff et al., 2013). The reduced production of B cells in BM, decreased numbers of pro-B and pre-B lymphocytes in blood (Rossi et al., 2003) and reduced numbers of B lymphocyte lead to reduced B cell help to T lymphocytes and less effective antibody response, essential to stamp out the SARS-CoV-2 virus promptly (McElhaney et al., 2020).

Cytokine IL-7 can improve the CD4+ naïve T cell response and has demonstrated effectiveness in sepsis and COVID-19 illness (Laterre et al., 2020; Monneret et al., 2020; Francois et al., 2018; Mackall et al., 2011). Thymosin alpha-1, (Tα 1), a synthetic thymic peptide, used in viral infections as an immune response modifier, reduced mortality of patients with severe COVID-19 illness (Liu et al., 2020; Wang et al., 2021). A clinical trial to treat COVID-19 in elderly patients with Tα1 was approved to commence early 2021. (https://clinicaltrials.gov/ct2/show/NCT04428008). The skewing of cytokine profiles towards the TH17 phenotype in COVID-19 might suggest that IL-17 blockers could provide a potential therapeutic strategy.

The lower numbers of CD4 lymphocytes and B cells in the immune profile in older people, puts them at considerable immune disadvantage and risk of life-threatening illness, when they develop SARS-CoV-2 illness (Cunha et al., 2020).

2.6. Dysregulation of cytokine network in ageing

The pro-inflammatory and anti-inflammatory cytokines are key molecular messengers that act immediately to activate an immune response in response to threats from the SARS-CoV-2 virus (Conti et al., 2020a; Mantovani et al., 2019; Rea et al., 2018). In older people, who are not overtly ill, the major pro-inflammatory cytokines such as IL-6, TNF-α, IL-1α and IL-12p40 are increased, with many researchers reporting similar age-related increases in pro-inflammatory cytokines (Franceschi et al., 2007, 2000; Forsey et al., 2003; Rea et al., 2000). Conversely, IL-10 and TGF-β, corresponding anti-inflammatory cytokines, show less consistent age-related change (Salminen et al., 2012; Minciullo et al., 2016; Kubiczkova et al., 2012). The gene and allele profile associated with pro-inflammatory and anti-inflammatory cytokines, is also important in each person's immune response, with alleles of the pro-inflammatory cytokine IL-6, for instance, showing different frequencies and expression depending on geographical location in Europe and globally, whereas the anti-inflammatory cytokine IL-10 and its alleles show differences between male and female nonagenarian subjects and mortality risk (Di Bona et al., 2009; Ross et al., 2003; Lio et al., 2003).

The chronic low-grade, sterile inflammation, characterised by increased levels of pro-inflammatory cytokines and mediators such as IL-6, IL-1β, TNF-α and C-reactive protein (CRP) in the circulation has been called 'inflamm-ageing', a term first coined in 2000 by Claudio Franceschi (Franceschi et al., 2000).

3. Why is morbidity and mortality so much higher in older people with COVID-19?

3.1. 'Inflamm-ageing' as we age fuels the cytokine storm

Immunosenesence and inflamm-ageing are high risk factors for severe COVID-19 illness in older people. The increased low-grade sterile inflammation, or inflamm-ageing, contributes to many age-related diseases such as atherosclerosis, rheumatoid arthritis, diabetes, neurodegeneration and ageing itself (Liberale et al., 2020; Ferruci and Fabbri, 2018; Rea et al., 2018; Franceschi et al., 2014). However, when SARS-CoV-2 illness co-exists with any or several of these age-related diseases, COVID-19 illness is much more severe and may become life-threatening (Akbar and Gilroy, 2020; Yang et al., 2020b; Bonafè et al., 2020).

Several molecular pathways and pattern-recognition receptors (PRRs) contribute to inflamm-ageing and ageing (Fig. 7). Toll-like receptors (TLRs) and Danger-Associated Molecular Patterns (DAMPs) use various intracellular signalling pathways, resulting in NF-κB activation and overproduction of cytokines, chemokines and IFNs. SARS-CoV-2 is sensed by the RNA-sensing endosomal PRRs, TLR 3, 7 and 8, the cytoplasmic-residing RIG-1-like receptors, and the mitochondrial mitochondrial antiviral-signalling protein (MAVS) signalome, but it interferes with normal production of anti-viral interferons (Wu et al., 2021; Jiang et al., 2020; Lei et al., 2020). Senescent cells and the associated secretome of senescence-associated-secretory-phenotype (SASP) increase with age and contribute to the inflammatory NF-κB pathway (De Francesco et al., 2020; Molony et al., 2017). Autophagy too is slowed up with ageing, causing damaged material to accumulate and trigger several signalling inflamm-ageing pathways (Stead et al., 2019; He et al., 2013).

The NLPR3 inflammasome-dependent response (Zhao and Zhao, 2020; Lee et al., 2020), activated by SARS-CoV-2 endosomal replication, oxidative stress, DNA damage, necrotic cell damage and multiple DAMPs, causes stimulation of the NF-kB- and IL-1β, IL-18, IL-33-mediated inflammatory cascade and adds to the cytokine-mediated hyperinflammation and cytokine storm, by further paracrine activation (Tay et al., 2020; Conti et al., 2020a; Salminen et al., 2012) (Fig. 8).

Although the term 'cytokine storm' has become widely synonymous with the self-perpetuating inflammatory cascade of severe COVID-19 illness, the mechanisms of COVID-19-induced lung injury and pathophysiology are still being clarified (Sinha et al., 2020), and no unifying

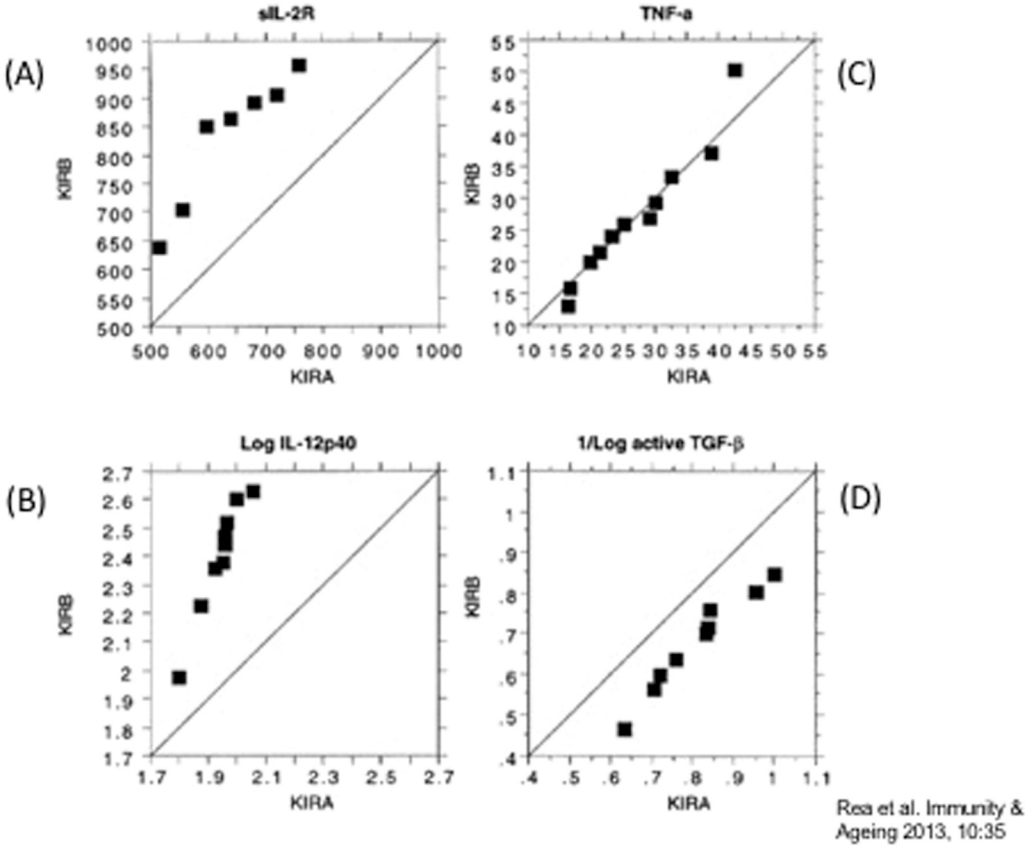

Fig. 5. Percentile plots for pro-inflammatory and anti-inflammatory cytokines, grouped by NK-related, Killer Immunoglobulin Receptor Haplotypes A and B (KIR A and KIR B), in Octo/Nonagenarians from BELFAST study. Killer cell Immunoglobulin-like Receptors (KIRs) are genetic markers on NK cells in individuals, that can be grouped into A and B haplotypes; KIR A haplotype has an inhibitory role, compared to the activating role of haplotype B, which produces pro-inflammatory cytokines. (A) shows percentile plot for NK cells grouped by KIR A haplotype on X-axis v KIR B haplotype on Y-axis for percentile values of serum sIL2-R in community-living octo/nonagenarian subjects; findings showing KIR B percentile values to the left of the 45° line, are consistent with KIR B haplotype-grouped NK cells producing sIL-2R, linked with pro-inflammation. (B) shows percentile plot for NK cells grouped by KIR A haplotype on X-axis v KIR B haplotype on Y-axis for percentile values of serum log IL-12p40 in community-living octo/nonagenarian subjects; findings showing KIR B values to the left of the 45° line, are consistent with KIR B haplotype-grouped NK cells producing IL-12p40, a pro-inflammatory cytokine. (C) shows percentile plot for NK cells grouped by KIR A haplotype on X-axis v KIR B haplotype on Y-axis for percentile values of serum TNF-α in community-living octo/nonagenarian subjects; findings showing KIR B values and KIR A values at or on the 45° line, are consistent with TNF-α being a neutral cytokine with respect to KIR A and KIR B haplotype-grouped NK cells. (D) shows percentile plot for NK cells grouped by KIR A haplotype on X-axis v KIR B haplotype on Y-axis for percentile values of log TGF-β in community-living octo/nonagenarian subjects; findings showing KIR B values to the left of the 45° line, are consistent with KIR B haplotype-grouped NK cells producing log TGF-β, with anti-inflammatory effects. NK cells produce both pro-inflammatory and anti-inflammatory cytokines, and balance is important in controlled innate immune responsiveness, homeostasis and repair. NKs, natural killer cells, BELFAST, Belfast Elderly Longitudinal Free-Living Ageing Study.

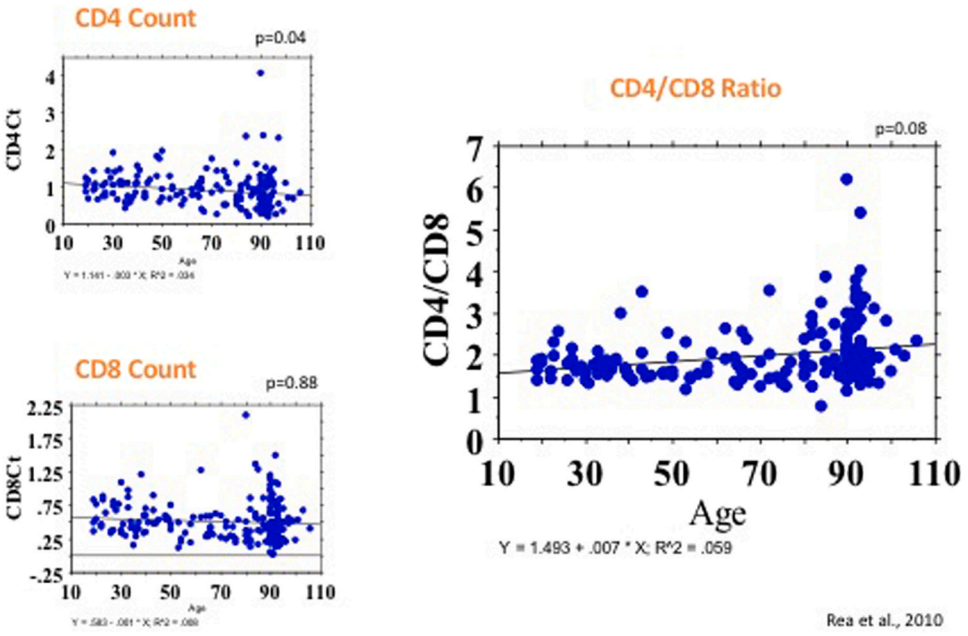

Fig. 6. Age-related changes in CD4+, CD8+ T cells counts and CD4/CD8 Ratio in Belfast Elderly Longitudinal Free-Living Ageing STudy (BELFAST). (A) Regression plot showing association for CD4+ T cell count with age, through 20–100 years. $R^2 = 0.034$; $p = 0.04$. (B) Regression plot showing CD8 +T cell count with age, through 20–100 years. $R^2 = 0.019$, $p = 0.88$. (C) CD4+/CD8+ Ratio and Age from 20 to 100 years. $R^2 = 0.059$, $p = 0.08$. All age participants recruited as part of Belfast Elderly Longitudinal Free-living Ageing STudy (BELFAST), were apparently well, community-living, mobilising independently, with no cognition impairment. $P = < 0.0001$ for difference between cell counts and age-related change for CD4+ and CD8+ subsets and age.

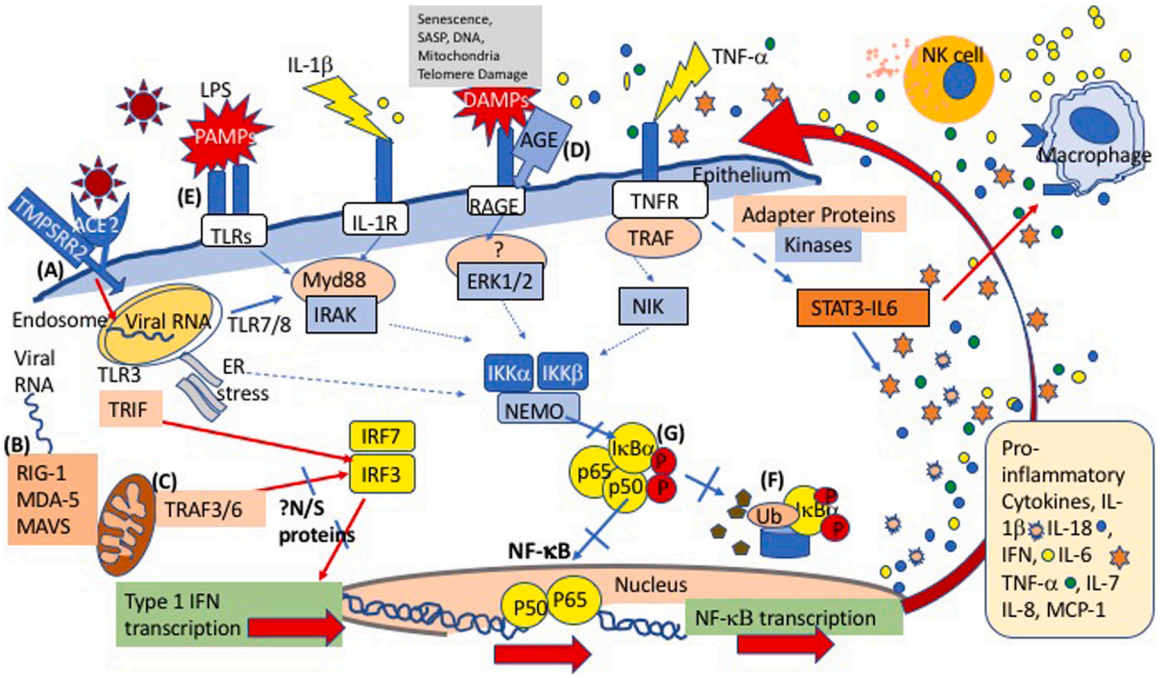

Fig. 7. Schematic diagram of molecular cellular pathways potentially involved in the NF-κB and IFN-signalling pathways, in SARS-CoV-2 illness. (A) SARS-COV-2 virus enters the alveolar cell via ACE2 receptor with help of TMPSRR2 protease, moves to the endosome where viral single-stranded DNA signals through TLR 7 and 8, and double-stranded DNA through TLR 3, to activate the NF-kB pathway via NEMO. (B) SARS-CoV-2, DNA, triggers the RIG-1-like receptors that act through interferon response elements, and interferes with normal production of anti-viral IFNs. (C) Viral SARS-COV-2 and ROS acting through mitochondrial MVAS pathway, reduces mitochondrial function and production of anti-viral interferons, possibly by use of its structural proteins. (D) Senescent cells, the associated secretome (SASP) and RAGE-associated-glycated damage join an inflammatory pathway involving the NF-kB, IL-1α, TGF-β, IL-6, that contribute to the pro-inflammatory milieu. (E) Secondary bacterial infections, such as pneumococcus, PAMPs and DAMPs use TLR4 and various intracellular signalling pathways, that result in NF-κB activation and further augmentation and production of cytokines, chemokines and interferons. (F) Autophagy is slowed up, causing damaged material to accumulate and trigger inflamm-ageing pathways. (G) All different signalling pathways join a common downstream signalling pathway that results in phosphorylation of the cytosolic inhibitor IκBα, which triggers its proteasomal degradation, resulting in translocation of NF-κB into the nucleus, with the production of the SARS-COV-2-related pro-inflammatory cytokine cascade. (H) Research trials are investigating repurposed drugs to block the NEMO/NF-κB pathway and proteosome inhibitors to block the autophagy process. TLR4, Toll-Like Receptor, LPS, Lipopolysaccharide; NEMO, NF-kappa B Essential Modulator; RIG-1-like, retinoic acid-inducible gene-I-like receptors; PAMPs, Pathogen Associated Molecular Patterns; DAMPs, Danger Associated Molecular Patterns; NLRs, nucleotide-binding and oligomerization domain receptors; NLRP3, NLR family pyrin domain containing 3; SASP, Senescence-Associated-Secretory-Phenotype; RAGE, Receptor for Advanced Glycation Endproducts; ROS, reactive oxygen species; MAVS, mitochondrial anti-viral signalling protein; TMPRSS2, transmembrane serine protease; BTK, Bruton's tyrosine kinase; NSAID, nonsteroidal anti-inflammatory drugs.

definition of cytokine storm exists. Fajgenbaum and June (2020), have proposed the following criteria: 1) elevated cytokine levels, 2) acute systemic inflammatory symptoms, and 3) secondary organ dysfunction, beyond that which could be attributed to a normal response to a pathogen, if a pathogen is present.

In COVID-19 illness, cytokine profiles stratify patients and likely outcomes (Lucas et al., 2020). Higher pro-inflammatory cytokines IL-1α, IL-1β, IFN-α, IL-17A and IL-12p70 provided a 'core' signature of severe COVID-19 illness, with lower levels of pro-inflammatory cytokines and early tissue repair proteins found in moderate illness. COVID-19 severe illness was further characterised by lymphopenia and the over-expression of molecules of inflammation (Matthew et al., 2020; Song et al., 2020; Tan et al., 2020a). Seriously ill COVID-19 patients showed impaired expression of pro-inflammatory cytokines and diminished mTOR signalling in myeloid cells and reduced IFN-α production by pDCs, both important first defences against viral replication and invasion (Arunachalam et al., 2020). The authors suggested that pDCs, the major producers of type 1 IFNs were impaired in COVID-19-infected patients, replicating findings of others (Sa Ribero et al., 2020; Schulte-Schrepping et al., 2020; Hadjadj et al., 2020; Chen et al., 2020a).

Administration of type 1 IFN has been proposed as a strategy for COVID-19 treatment (Wang et al., 2020a; Sallard et al., 2020; Zhou et al., 2020b; Abdolvahab et al., 2021). Two trials have reported. Monk et al. (2021), in a meta-analysis, demonstrated reduced length of hospitalisation with inhaled or interferon-beta-1α (Synairgen), and Fu et al. (2020) demonstrated good clinical improvement using combined inhaled IFN-γ with TTK, a small peptide that enhances mucosal healing, in COVID-19 patients. Sosa et al. (2021), in a systematic review of evidence, demonstrated reduced length of hospital stay with IFN-β use, in COVID-19 patients.

The production of Type I IFNs, a key defence against COVID-19 is reduced in COVID-19 patients. Clinical improvement and length of hospital stay was reduced in clinical trials, with careful use of type 1 IFN, early in illness.

3.2. *The inflammation pathway fails to resolve in COVID-19*

Inflammation is induced when NK cells and macrophages detect infection from protein-associated molecular patterns (PAMPs) associated with the SARS-CoV-2 virus. Danger-associated molecular patterns (DAMPs) are also triggered by host-derived stress signals such as ATP, nuclear proteins and cytokines including the extended IL-1 family of cytokines that amplify the very exuberant damage response stimulated by the host's NK cells response to the SARS-CoV-2 virus (Li et al., 2020b; Tay et al., 2020; Cicco et al., 2020). Pro-inflammatory cytokines, arachidonic acid-derived prostaglandins and leukotrienes increase vascular permeability, allowing macrophages and neutrophils to migrate across venules to sites of SARS-CoV-2 invasion in the lung and continue the cycle of phagocytosis and killing, fibrin deposition and possible capillary thromobosis.

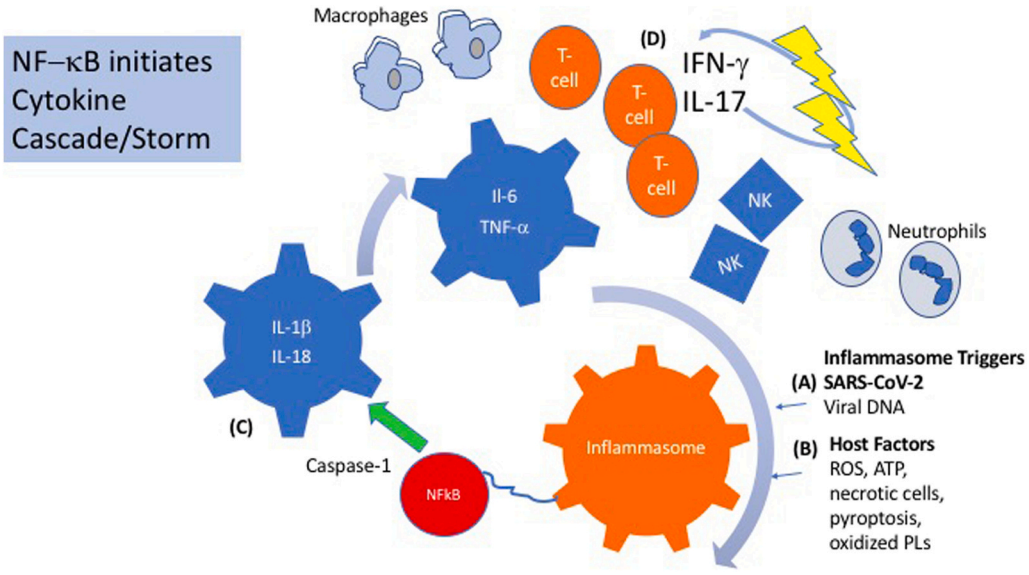

Fig. 8. Inflammasome NLRP3 initiates the cytokine cascade/storm using NF-kB pathway. (A) Direct stimulation of inflammasome NLRP3 is triggered by viral protein from SARS-CoV-2 through TLR 3 signalling. (B) Non-direct stimulation occurs through host-intrinsic mechanisms such as DAMPS - oxidation of phospolipids from alveolar epithelial/endothelial membranes, ROS, ATP, necrotic cells and pyroptosis. (C) NLRP3 inflammasome activation induces the production of mature IL-1β and IL-18 from inactive pro-IL-1β and pro-IL-18 precursors by caspase-1, which initiates a cytokine cascade. (D) The pro-inflammatory cytokines including L-6, IL-2, TNF-α, in turn stimulate production of IL-17 and IFN-γ which can activate the JAK-STAT or NF-κB signalling via binding to their receptors expressed on immune cells, to induce more production of pro-inflammatory genes, forming a positive feedback to trigger hyperinflammation and the threshold of cytokine storm. TLR3, Toll-Like Receptor 3; NLRP3, NLR family pyrin domain containing 3, DAMPs, Danger Associated Molecular Patterns; ROS, Reactive Oxygen Species; ATP, Adenosine Triphosphate; PLs, phospholipids; JAK-STAT, Janus kinase-signal transducer and activator of transcription.

In older age, the molecular and cellular processes that normally damp down inflammation, such as the anti-inflammatory cytokine families of IL-10 and TGF-β, soluble receptor antagonists, microRNAs, the resolvin family of bioactive molecules and pro-resolving monocyte-derived macrophages become less ineffective in stopping the inflammatory cascade. Resolution and repair seem to be seriously inadequate in some COVID-19 patients (Fig. 9).

The continuous breakdown of cellular products and DAMPs-related pro-inflammatory molecules produces a constant cycle of entry and re-entry into self-perpetuating and damaging pro-inflammatory cytokine pathways (Fig. 9).

3.3. SARS-CoV-2 virus-induced inflammatory response in the lung is accentuated in ageing

COVID-19 has major effects on the lungs and airways and the lung is at the centre of the SARS-CoV-2 cytokine storm. Advanced age is a leading risk factor for developing acute respiratory distress syndrome (ARDS), a life-threatening event, requiring ICU admission (Hu et al., 2021; Du et al., 2020). In elderly individuals reduced lung volume and elasticity, increased fibrosis and inflammation from smoking, environmental toxin exposure/s, and multiple disease pathologies, result in markedly reduced respiratory function that compromises oxygen blood gas exchange, and make it more difficult for older patients to overcome COVID-19 illness and respond to ICU ventilation (Thomas et al., 2019;

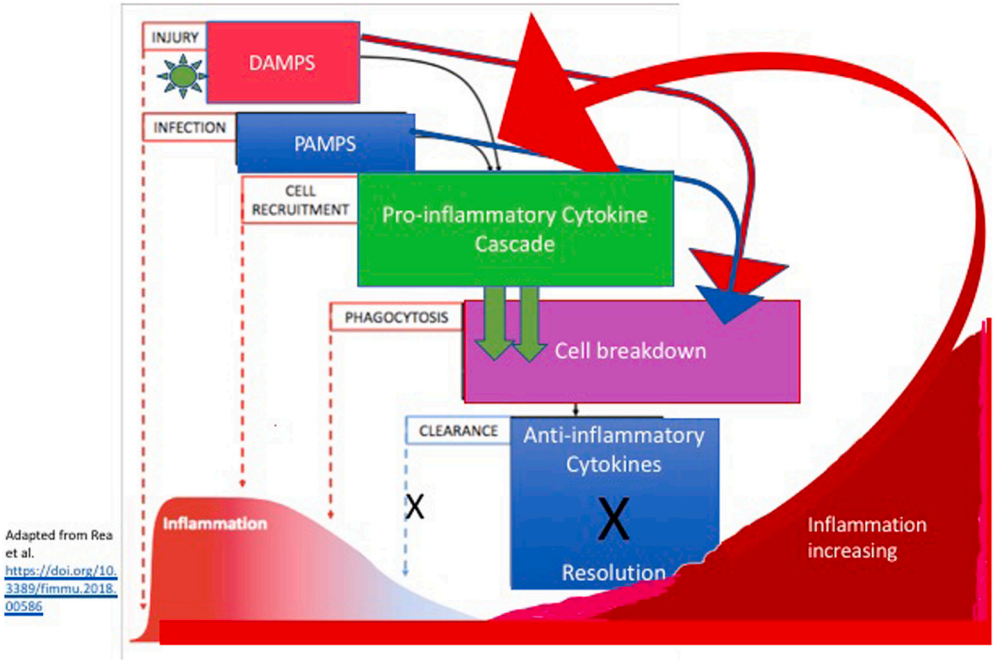

Fig. 9. The cycle of non-resolving inflammation leading to self-perpetuating cell breakdown and the cytokine storm. The cycle of injury begins when antigen from the SARS-Cov-2 virus is detected by DAMPS and then by PAMPs which are triggered by host-derived stress molecules, such as damaged nuclear proteins. NK cells' release of cytotoxic materials, together with DAMPs and PAMPs trigger a pro-inflammatory cytokine cascade of the IL-1 family of cytokines and multiple pro-inflammatory molecules. The resolution of inflammation by resolvins and anti-inflammatory cytokines is unable to commence promptly and a cycle of self-perpetuating, self-destructive inflammation is triggered, causing cell and multi-organ damage and possible death. DAMPS, danger -associated molecular patterns; PAMPs, protein-associated molecular patterns; NKs, natural killer cells, SARs-CoV-2.

Turner et al., 2017; Yoon et al., 2019; Kim et al., 2017) (Fig. 3A, B).

3.3.1. Alveolar epithelial cells and alveolar macrophages and ageing

Ageing causes senescence and metabolic alterations in AT11 cells that reduce regeneration after acute lung injury, such as COVID-19 (Brandenberger et al., 2018; Yazicioglu et al., 2020). There are age-related changes in alveolar epithelial type 1 (AT1) cells that normally maintain the epithelial-endothelial barrier preventing protein fluid leakage across the alveolar wall into the air spaces, while allowing gases to freely cross the air-blood barrier (Byrne et al., 2015). The lung tissues lose elasticity, risking collapse and alveolar sacs become baggy, both influencing gas exchange and patient outcome in COVID-19, and when receiving ICU ventilation (Fig. 3B). The age-related decrease in alveolar macrophage numbers and function (Linehan et al., 2015) is likely important, as the monocyte infiltration that they recruit, peaks between days 5–7, and could become delayed in the older COVID-19 patient, pausing initiation of an effective immune response.

3.3.2. Tissue-resident T cells (T_{RM}) in lung

$T_{RMs,}$ holding memory from a previous SARS-CoV-2 or related-coronavirus infection, can 'kick start' immune responses to a new COVID-19 infection (Grau-Expósito et al., 2021; Golpen et al., 2021; Kok et al., 2020) (Fig. 3C). The discrete immunostatic balance between alveolar macrophages, NK and CD8 T_{RM} memory cells can become easily disturbed and overactive in lungs already damaged by chronic disease, with increases in CD8 T_{RM} cells causing augmentation of inflammation, influx of fibrosing fibroblasts, resulting in damaging fibrosis and reduced lung function in the COVID-19-ARDs patient (Mora-Buch and Bromley, 2021; Goplen et al., 2020). In fulminant COVID-19, more common in elderly patients, the epithelial-endothelial barrier becomes damaged and platelet/fibrin microemboli form, with risk of thrombosis and multi-organ damage (Fig. 3D–F).

While TRMs have the potential to augment the hyperinflammatory immune response, in COVID-19 illness, the presence of SARS-CoV-2-N-specific-T_{RM} cells in some patients suggests the possibility of being able to induce stable and highly reactive vaccines.

3.4. Reduced type 1 IFN and IFN genetics play a role in COVID-19

Interferon and members of the type I IFN family interfere with viral replication and are essential for an effective antiviral response. Reduced type 1 IFN secretion contributes to weaker immune responses in older people during phase 1 of the immune response (Wells and Coyne, 2018). Research shows there are genetic and antibody explanations for some of the excess mortality among patients with severe COVID-19, and for increased risk in males and older age groups.

Clues into genetic mutations in COVID-19 illness were identified by comparing DNA from brother-pairs, severely ill with COVID-19; there were genetic and gender differences of genes involved in IFN production (van der Made et al., 2020). Inborn errors of TLR3, vital in viral recognition and activation of innate immunity, and IRF7-dependent type-I IFN critical in immunity against viruses, were pin-pointed as DNA markers. In these patients, IFN immune response was insufficient to suppress early COVID-19 infection, allowing SARS-CoV-2 virus to trigger widespread immune reaction and disastrous lung-injuring, inflammatory-collateral damage and death (Blanco-Melo et al., 2020).

The COVID Host Genetic Effort (2020) (https://www.covidhge.com), also reported loss-of-function (LOF) variants, previously known to compromise TLR3- and IRF7-dependent type 1 IFN immunity to influenza and childhood pneumonitis (Casonova et al., 2020; Zhang et al., 2020). The genetic mutations, carried on the X-chromosome affected males and inhibited IFN production directly or indirectly, and although rare, occurred at all ages, including at older ages. A distinct COVID-19 phenotype characterised by absent IFN-β and low IFN-α production and activity and partially driven by the NF-kB cytokine pathway (Hadjadj et al., 2020), explained, in part, how deleterious mutations in the human IRF7-dependent type 1 IFN immunity caused severe COVID-19 illness.

Antibodies to IFN, newly recognised in life-threatening COVID-19 pneumonia in 2.6% of women and 12.5% of men (Bastard et al., 2020), were found at all ages, and the autoantibody abnormality was clinically silent before patients developed COVID-19 (Zhang et al., 2020: Hadjadj et al., 2020). Possible treatment options include blocking/removing damaging antibodies by plasmapheresis or specific inhibition of type 1 IFN-reactive B cells.

Of the six genes identified, by The COVID-19 Host Genetics Initiative (2020a,b) on chromosome 3, SLC6A20 encoded a transporter that interacts with ACE2, the SARS-CoV-2 cell receptor, and others encoded chemokine receptors. A signal at 9q34.2 coincided with ABO blood group locus previously shown to have higher risk for blood group A carriers and a protective effect for blood group O, in non-genetic studies (Zhao et al., 2020). In a further twist, Zeberg and Pääbo (2020), reported that the chromosome 3 gene cluster, found in life-threatening COVID-19, (The Severe COVID-19 GWAS Group 2020), matched chromosome 3 haplogroup in Neanderthals, inherited 50,000 years ago. Today this gene haplotype is carried by ≈ 30% South Asians, 8% Europeans and 4% admixed Americans, but rarely in East Asians and Africans, and is the gene area associated with increased risk of severe COVID-19 (Public Health England, 2020). Heterozygous or homozygous carriers have ≈ 1.5–3 times increased risk compared to non-carriers, which may link with increased COVID-19 severity, in certain present-day populations (Zeberg and Pääbo, 2020).

Genetic research aids understanding about the complex effect that COVID-19 has on the immune system and has focused clinicians to identify vulnerable individuals by screening for IFN-related genes, IFN-related autoantibodies, and to establish trials using type 1 IFNs in selected patients, at different times in the course of SARS-CoV-2 infection. Recent understanding suggests that appropriate and timely interaction between Type 1 and Type 11 IFNs is important in controlling SARS-CoV-2 viral replication and avoiding uncontrolled inflammation and excess tissue death.

3.5. The ACE2 doorway

The SARS-CoV-2 virus enters the host cell by using ACE2 as an entry receptor, and two host transmembrane serine proteases TMPRSS2 and neuropilin-1 help prime the SARS-CoV-2 spike (S) protein to allow entry into the host cell (Hoffman et al., 2020; Daly et al., 2020). The renin-angiotensin-aldosterone system (RAAS) is considered to play an important role in the pathogenesis of COVID-19 infection (Ingraham et al., 2020) (Fig. 1A–C). The ACE2 gene influences the renin angiotensin system (RAS) function by modulating blood pressure, sodium and fluid balance and may thereby be important in COVID-19 patients with cardiovascular and renal disease (Narula et al., 2020; Guo et al., 2020; Shi et al., 2020).

3.5.1. Hypertension and ACE and ACE2 polymorphisms

Since the start of the COVID-19 pandemic, researchers and clinicians have noticed an increased severity of SARS-CoV-2 disease in patients with cardiovascular disease and hypertension (Clerkin et al., 2019; Bonow et al., 2020). Given the importance of the ACE receptor for SARS-CoV-2 access into the cell, ACE polymorphisms might be important in COVID-19 susceptibility. The DD homozygous allele of the insertion/deletion (I/D) polymorphism of the ACE gene has been previously investigated as a risk factor for hypertension and cardiovascular disease, the outcome in ARDS, and progression of pneumonia in Middle Eastern SARS (Evans et al., 1994; Matsuda et al., 2012; Itoyoma et al., 2004) and was considered a possible risk for severe COVID-19 disease. Yamamoto et al. (2020), reported that SARS-CoV-2 cases and mortality were negatively associated with the ACE II genotype, and that ACE I/D polymorphism may be a genetic marker for SARS-CoV-2 infectivity and pathogenicity, dependent on patient geo-location. The ACE II

homozygote frequency varies widely East to West, with higher frequencies in Japan (48%), Korea and China (41%) compared to Spain (15%) and 18% in Europe. Serum levels of ACE are higher in DD genotype carriers (Rigat et al., 1990) suggesting that normal homoeostasis that is controlled by the functional balance between ACE /ACE 2 genes, may be compromised by SARS-CoV-2's use of the ACE2 receptor, resulting in over-activation of ACE pathway of the RAAS system, causing endothelial dysfunction, microthrombi, pulmonary shut-down, severe critical illness and death (Fig. 1).

Bosso et al. (2020) demonstrated that 12 variants of the ACE2 gene were associated with risk of hypertension and/or cardiovascular disease. Meta-analyses across different populations confirmed hypertension risk in carriers of the rs2285666 polymorphism (Niu et al., 2007; Lu et al., 2012). This polymorphism demonstrated higher allele frequency (0.556) in the China Metabolic Analytics Project (China MAP) populations compared to Mixed American, 0.336; African, 0.211; European, 0.235 and Indian populations (0.6) (Cao et al., 2020a; Srivastava et al., 2020), with similar population findings by (Hou et al., 2020).

ACE inhibitor (ACEi) and angiotensin receptor blockade (ARB) drugs are commonly used medications for high blood pressure and for diabetic patients with co-existing renal disease, leading to concerns that these drugs, would increase susceptibility to SARS-CoV-2 infection (Mogensen et al., 2000; Fang et al., 2020). Several observational studies have not demonstrated any adverse association between medication use and risk of increased mortality, though variations between different ethnic groups did raise the possibility of ethnic-specific effects of ACE inhibitors/ARBs on COVID-19 disease susceptibility and severity (Hippisley-Cox et al., 2020; Straw and Witte, 2020). Current clinical advice is to continue the use of ACEi and ARB medication in COVID-19 patients, as medication may help support the cardiovascular system (Jarcho et al., 2020; Morales et al., 2021).

Both ACE2 and ACE polymorphisms vary across the world (Asselta et al., 2020; Cao et al., 2020a). Taken together, the differences in allele frequencies of ACE and ACE2 variants may compromise the functional balance in the RAAS system and relate to COVID-19 morbidity and mortality across different populations and ethnicities (Lippi et al., 2020).

3.6. Obesity and diabetes

COVID-19 death rates are 10 times higher in countries where more than half of the adult population is overweight, compared to countries where populations are within normal weight guidelines (The World Obesity Federation, 2021). In 160 countries, there were linear correlations between a country's COVID-19 mortality and the proportion of overweight adults. The report builds on previous analyses demonstrating that obesity is an independent risk factor of severe illness and death from COVID-19 (Wise, 2021; Popkin et al., 2020; Global Burden of Disease, 2019). The UK OpenSAFELY analysis (Williamson et al., 2020) also demonstrated a dose-response relationship between excess weight and severe COVID-19 after adjusting for age, sex, ethnicity and social deprivation, with studies from Europe, Asia and USA confirming similar findings (Petrilli et al., 2020; Huang et al., 2020b). The prevalence of being overweight and being obese approaches 60–70% in the UK and US and contributes to high blood pressure, type 2 diabetes and heart disease, that associate with the highest morbidity and mortality in SARS-CoV-2 patients, particularly in males (Holman et al., 2020; Li et al., 2020a; Sattar et al., 2020).

Older people, while not necessarily fitting criteria for obesity, do demonstrate disproportionate increases in body fat percentage due to muscle loss because of sarcopenia (Dutra et al., 2017; Batsis et al., 2016). Fat cells contribute to inflamm-ageing and impair the immune system at the molecular level by producing pro-inflammatory cytokines such as TNF-α (Frasca et al., 2017), and also reduce the physiological ability of the lung to clear airway infection, as for example in influenza or COVID-19. The high levels of ACE2 gene expression present in the large number of fat cells in obesity, serve as a hidden reservoir for the SARS-CoV-2 virus, facilitating spread to other organs, causing severe COVID-19 inflammation, multi-organ failure, and increased mortality (Al-Benna, 2020; Kruglikov and Scherer, 2020).

Diabetes, one of the main risk factors associated with COVID-19, is linked with obesity and increases with age. Diabetes doubled the risk of death for those with reduced diabetic control, with similar findings and outcomes in patients with pre-existing type 2 diabetes and COVID-19 (Williamson et al., 2020; Zhu et al., 2020; Yang et al., 2020a). The hazard-ratio increased by 4 times if renal function was markedly reduced. An analysis of the most common co-morbidities of patients in ICUs with COVID-19 were hypertension (23·7%) and diabetes mellitus, further confirmed by data collation of mortality and co-morbidities in 52 ICUs (Guan et al., 2020; Fang et al., 2020). With improved follow-up of COVID-19 patients, new-onset diabetes has been identified as a post-COVID-19 illness and a monitoring group-CoviDIAB Project (covidiab.e-dendrite.com), will investigate the bidirectional relationship between COVID-19 and new-onset diabetes (Rubino et al., 2020; Lim et al., 2021).

Patients with COVID-19, and those with the metabolic syndrome (a combination of obesity, high blood pressure, diabetes), were almost 5 times more likely than their peers to require intensive care and ventilation, and 3–4 times more likely to die from COVID-19 illness (Xie et al., 2021a).

3.7. Age and gender

Age and gender are well-established risk factors for morbidity and mortality from SARS-CoV-2 infection. The data from China demonstrated greater numbers of male patients in hospital with SARS-CoV-2 illness, and male sex was an independent risk for disease and death (Zhou et al., 2020a). In Italy, men represented 58% of COVID-19 infected patients and 70% of COVID-19-related deaths (Remuzzi and Remuzzi, 2020). The UK openSAFELY data-analysis demonstrated that 90% of COVID-19-related deaths were in people > 60-years-of -age and 60% were male (Williamson et al., 2020). According to the authors, males have an overall 1.6-fold increased risk of death compared to female patients in the UK, with similar findings globally (Dehingia and Raj, 2021).

The reason for the sex-related increase in COVID-19-related deaths has been much considered. The ACE2 gene, is present on the X gene, and the double 'dose' of ACE2 on XX genes which females carry, may provide some advantage, such as increased ACE2 receptor coverage in the lung where it could protect from ACE-related damage in COVID-19 infection (Gemmati et al., 2020). According to Chen et al. (2020a,b,c), ACE2 expression in the lung was highest in children and young people and increased by oestrogen and androgen; conversely ACE2 expression decreased with age and was lower in hypertension, cardiac hypertrophy and cardiac failure, co-morbidities that increased COVID-19 risk (Luo et al., 2019; Sama et al., 2020; Gebhard et al., 2020).

Females and males differ in incidence, susceptibility, response and disease severity in viral infections (Klein, 2020; Mauvais-Jarvis et al., 2020; Klein and Flanagan, 2016). Males are more vulnerable, across a range of diseases throughout life, including in old age (Hirokawa et al., 2013; Wang et al., 2015; Bonafè et al., 2020). Generally, females mount stronger innate and adaptive immune responses than males, that results in faster clearance of pathogens and greater vaccine efficacy in females than in males. However, contraintuitively, higher innate cytokine responses- IL-18 and IL-8- were demonstrated in response to COVID-19 illness in males, whereas female patients developed higher T cell activation, whichaccording to the authors might explain the sex-related differences in COVID-19 outcome (Takahashi et al., 2020).

Sex hormones influence the immune system (Auerbach and Khera, 2021; Taneja, 2018), fall with age and are decreased by multiple age-related co-morbidities (Traish et al., 2015), with evidence of improvement following hormone replacement treatment (Yassin et al.,

2019; Baillargeon et al., 2019). Sex steroids bind to immune-cell steroid receptors, influence signalling pathways, including NF-κB and interferon regulatory factor (IRF) 1, resulting in production of cytokines/chemokines (Bereshchencko et al., 2018). Sex differences could be caused by imbalanced gene expression encoded on the X and Y chromosomes, mediated by sex differences in the XX gene dose or parental epigenetic imprinting, resulting in incomplete X inactivation (Mauvais-Jarvis et al., 2020).

Male sex was an independent risk for disease and death from COVID-19. Sex differences could be caused by sex hormones and imbalanced gene expression encoded on the X and Y chromosomes.

3.8. Behaviour, culture and geography

Behaviour, culture and geography influence COVID-19 infections and the severity of illness. Past and current smoking behaviours, previously higher in men compared to women, have contributed to chronic obstructive pulmonary disease (GBD 2015 Tobacco Collaborators, 2017; Jamal et al., 2016), and increased risk of death in COVID-19 illness (Alqahtani et al., 2020; Khalil et al., 2021). Males have a greater life-time burden of cardiovascular risk compared to females, that also contributes to their differential risks of serious COVID-19 illness compared to females (Walli-Attaei et al., 2020). Females also benefit from the early vascular protection provided by pre-menopausal hormones (EL Khoudary et al., 2020; Aggarwal et al., 2018). Obesity affects both sexes. The World Obesity Federation (2021) report demonstrates population obesity is highly associated with a country's COVID-19 mortality. The evidence calls for vaccination priority related to obesity and for strong government control measures, to stop industry-based-food production, that contributes to population obesity and poor health (Tan et al., 2020b).

Data from Public Health England (PHA) has shown correlation between rates of COVID-19 cases/100,000 residents and average life expectancy, so that cities with lower life expectancy rates also track with higher rates of COVID-19 illness (Public Health England, 2020). The Office for National Statistics (ONS, 2020a,b) reported similar associations between the social determinants of health and COVID-19 illness in 2020. Similar findings were described in the US by van Dorn et al. (2020) writing that "*people's health is directly related to the conditions in which people are born, grow up, work and age and that social injustice is the biggest killer of all*", findings that mirror the frequently re-iterated message in the UK by Marmot et al. (2008), relating to 'social determinants of health'. Similar calls for equity and social justice alongside public health actions are being called for, across continents (Smith and Judd, 2020; Rollston and Galea, 2020).

Altogether, the evidence shows that after adjusting for age, most differences in COVID-19 mortality could be explained by demographic, geographical and socio-economic factors, such as home location and occupation (Golestaneh et al., 2020; Haynes et al., 2020).

3.9. Vitamin D

The possibility that vitamin D supplements could reduce susceptibility to and the severity of illness with COVID-19 seems a simple solution, particularly since older people are often vitamin D deficient, but robust and convincing evidence remains elusive. A series of smaller studies have shown relationships between vitamin D deficiency and severity of COVID-19 illness and death (Laird et al., 2020; Ilie et al., 2020; Ali, 2020). Conversely, Hastie et al. (2020) using retrospective Biobank data from half a million people, found no association between vitamin D and COVID-19 infection, with similar findings from the OpenSAFELY data (Williamson et al., 2020), and from an Australian randomised clinical trial, of vitamin D and severity in non-COVID-19 respiratory infections in older people (Pham et al., 2021). An updated meta-analysis (Teshome et al., 2021), found a sufficient Vitamin D level was associated with a decreased risk of COVID-19 infection.

In an interesting approach, lower vitamin D associated with COVID-19 mortality dependent on participant geographical North/South latitude (Whittemore, 2020; Pereira-Santos et al., 2019; Rhodes et al., 2020). People with darker skins, those with excess body fat, older people and carriers of the GC (group-specific component) vitamin D receptor rs4588 AA genotype were also more likely to become vitamin D deficient (Kohlmeier, 2020). The A allele variant of rs4588, particularly common in people with caucasian ancestry, demonstrated 36% lower vitamin D levels in the 8% of the population, who are homozygous carriers (Jiang et al., 2018).

Vitamin D affects the immune system and has been considered to protect against respiratory infections (Martens et al., 2020; Chambers and Vukmanovic-Stejic, 2021; Martineau et al., 2017). It acts through receptors on T and B cells to modulate the adaptive and innate immune response through signalling pathways, by suppressing Th-1 cell proliferation, by decreasing production of pro-inflammatory cytokines, IFN-γ and IL-2 and reducing antigen presentation by DCs (Bscheider et al., 2016; Martens et al., 2020). Overall, vitamin D polarises the adaptive immune system away from Th-1 and towards Th-2-related immune responses. Recent research showed that Vitamin D-deficient, COVID-19 patients had worse outcomes compared with aged-matched, vitamin D-replete patients, with signs of increased cytokine release syndrome (Daneshkhah et al., 2020). and ongoing need for ventilatory support (Baktash et al., 2020).

An updated Cochrane review found inconsistent evidence regarding an association between vitamin D deficiency and COVID-19 severity (Stroehlein et al., 2021). Meanwhile, as the debate continues, current advice has encouraged use of vitamin D3 supplementation of 600 IU daily, at least during the darker, colder days of winter and spring, in keeping with wider clinical opinion (Vimaleswaran et al., 2021; National Institute of Clinical Excellence (NICE), 2020).

4. How could immunocompetence in older and frailer populations be strengthened and supported to improve protection from COVID-19 illness?

4.1. SARS-CoV-2-reactive T cells

One of the most important questions about COVID-19 infection, is whether SARS-Cov-2 virus stimulates T cell memory, likely to protect people and provide long-term immunity. Immune studies in COVID illness have begun to answer this question.

Weiskopf et al. (2020) demonstrated that SARS-COV-2-reactive T cells were present and increased over time in ventilation-supported, severely ill COVID-19 patients. Further supporting evidence was presented by Braun et al. (2020) who demonstrated S-protein-specific CD4+ T cells in 83% of patients with COVID-19, but also in 34% of seronegative healthy donors. Grifoni et al. (2020) used large-scale testing with HLA class 1 and 11 peptide 'megapools' and identified SARS-CoV-2-specific CD8+ and CD4+ T cells in approximately ≈ 70% seronegative COVID-19 individuals and 100% of convalescent COVID-19 patients respectively, with robust CD4+T cell responses to S spike, the main target of vaccine efforts. The authors suggested that some T cells induced by common cold coronaviruses could cross-react with the SARS-COV-2 viral antigens.

In another series of studies with a different emphasis, Peng et al. (2020) demonstrated a greater breadth and magnitude in memory T cell responses from convalescent individuals in severe, compared to mild cases, for spike S, M, and ORF3, SARS-CoV-2 proteins. Research, by Kusnadi et al. (2021), demonstrated that CD8+ T cells in milder cases showed T cell exhaustion, whereas SARS-CoV-2-reactive cells in severe COVID-19 showed transcripts linked to co-stimulation, pro-survival NF-κB signalling, and antiapoptotic pathways, suggesting robust CD8+ T cell memory. In a longer follow-up, SARS-CoV-2-specific CD4+ and CD8+ memory T cells were present at 7 weeks, and interestingly, SARS-CoV-2-specific memory T-cell were also present in contacts,

exposed to, but not infected by virus Wang et al. (2021b).

Despite studies showing that T cell reactivity to SARS-CoV-2 was present in individuals recovering from COVID-19 infection or in unexposed individuals, perhaps due to cross-reactivity with the common cold coronaviruses, it is not known how long this immunity will last, and if it can continue to influence clinical outcomes in SARS-CoV-2 infection in patients, irrespective of age. Could the mild or asymptomatic presentation of Covid-19 illness in young children be related to their frequent exposure to common cold and respiratory illness during childhood and produce useful cross-reactivity to SARS-COV-2 infection? Research in previous SARS animal models suggested that cross-reactive airway CD4+ T cells might be of value in protective immunity to coronaviruses (Zhao et al., 2016). Similar findings were described by Dan et al. (2021), who demonstrated that pre-existing reactivity against SARS-CoV-2 came from cross-reactive T cells that can specifically recognise a SARS-CoV-2 epitope as well as the similar epitope from common cold human coronaviruses. Le Bert et al. (2020), too, in a comparative study of T cell responses to SARS-CoV-2 structural proteins, between recovering COVID-19 and uninfected subjects, demonstrated increased NSP7 and NSP13 proteins in uninfected patients, similar to those found in animal betacoronaviruses, suggesting cross-reactivity; additionally, the authors demonstrated long-lasting memory T cells, that reacted to the N protein of the previous SARS-CoV virus, and could be detected in recovered SARS patients, 17 years later, providing suggestive evidence that COVID-19 patients would likely develop long-term T cell immunity.

To date, there is increasing evidence that COVID-19 develops SARS-Cov-2-specific-T cell immunity that can last up to 6 months.

4.2. Bystander activation linked to vaccination

Live attenuated vaccines given to patients may extend the patient's immunity to other viruses for several months (van Aalst et al., 2017). For years bacille Calmette-Guérin (BCG for tuberculosis) and measles vaccines have been used as a mechanism to reduce all-cause mortality, with evidence that bystander effects of vaccination reduced infectious disease mortality by 40% in neonates (Benn et al., 2020; Moorlag et al., 2019; Biering-Sørensen et al., 2017). In a systematic analysis, Yitbarek et al. (2020) described the incidence and death from acute respiratory infection including COVID-19, was significantly lower in countries with universal BCG vaccination, but called for further evidence. In a related study, Gursel and Gursel (2020), demonstrated that COVID-19 cases/million and deaths/million were significantly lower in countries with, as compared to those without, BCG vaccination programmes, and reported that BCG vaccination-induced, non-specific protective effects could be long-lasting (~ 20 years), with the potential to influence SARS-CoV-2-associated community spread and/or disease severity. A short Israeli study compared SARS-CoV-2 infection rate between previously BCG-vaccinated and non-vaccinated young adults and found no difference in positivity or severity of infection (Hamiel et al., 2020), whereas the Activate randomised clinical trial of BCG-vaccinated, compared to non-BCG-vaccinated elderly people, showed a reduction of ≈ 45% against a range of non-COVID-19 respiratory infections (Giamarellos-Bourboulis et al., 2020a,b).

Influenza has a resemblance to SARS-COV-2 virus, sharing similar approaches to control interferon-stimulated-gene (ISG) responses (Menachery et al., 2014) and the use of ACE2 receptors in the lung (Liu et al., 2014). An analysis, linking recent influenza vaccination and data from 34 countries from the Organisation for Economic Cooperation and Development (OECD) and COVID-19-related mortality, morbidity and case incidence in adults > 65 years, suggested that influenza vaccination (H1N1) appeared protective, with a mortality benefit of ≈ 30% (Arokiaraj, 2020). The author further suggested that *Streptococcus pneumonia* vaccination, with similar mortality benefits, be included in vaccination strategies, for older people where immunity was lower (Brooks and Mias, 2018). Although the cause of this extended immunity to viruses after live-attenuated virus inoculation is not properly understood, activation of the surrounding memory T cells may be beneficial to the immune system as it may prime or strengthen the memory T cell repertoire (Li Causi et al., 2015; Di Genova et al., 2010, 2006) in an immune-related hormesis-type-effect by contributing to immune tolerance/resilience and decreasing the extent of infection-related tissue damage, through possible epigenetic changes (Calabrese, 2016; Weis et al., 2017; Kleinnijenhuis et al., 2012).

Altogether, evidence points to a possible protective and all-cause mortality benefit from the non-specific effects of influenza and/or pneumococcal vaccination in older people, when used as an adjunct strategy to improve protection from serious COVID-19 illness.

4.3. Neutralising antibodies and COVID-19 illness

Convalescent plasma, hyperimmune globulin and synthesised monoclonal antibodies are based on the same principle of using natural or manufactured antibody to stop and neutralise the virus. Antibodies, whether human-derived or laboratory-manufactured, last for some weeks and then decline, but they can help hold the seriously ill patient stable, while their own immune system recovers well enough to effectively to deal with the SARS-COV-2 virus threat.

Small studies using convalescent serum for SARS-CoV-2 patients suggested that treatment was well tolerated, reduced viraemia and clinical symptoms (Shen et al., 2020; Duan et al., 2020), whereas the larger RECOVERY Collaborative Group (2021c), testing convalescent plasma as a treatment in life-threatening COVID-19 did not result in significant improvement and was discontinued early. Early clinical donor convalescent studies may not have been consistent with Federal Drug Association (FDA) guidelines (US FDA, 2020), since donor convalescent serum antibodies are higher in males compared to females and after severe COVID-19 illness, and studies may not have been comparable (Klein et al., 2020; Chen et al., 2020b). In an editorial update, Katz (2021), proposed that any use of convalescent plasma should be considered in early infection; whereas an updated meta-analysis reported that convalescent plasma did not provide improved survival or other positive outcomes for COVID-19 patients (Janiaud et al., 2021).

Synthetic monoclonal antibodies have been developed and have been used in the treatment of COVID-19 illness. The apparently successful use of a laboratory-made neutralising antibody in the early days of COVID-19 treatment of a former US President, was followed by the publication of data from a small Regeneron trial. The, two-drug-cocktail, contained casirivimad and imdevimab, both proteins that bind to the surface spike S protein and block the virus attachment to the ACE2 receptor (Baum et al., 2020). In a clinical trial of non-hospitalised people, positive for SARS-CoV-2, treatment with REGN-COV2 showed reduced viral carriage and improved clinical outcomes (Weinreich et al., 2021). Drug concentrations were detected at 29 days in almost all patients and the long half-life of REGN-COV2 treatment suggested passive immunity lasted several months. Another monoclonal antibody LY-CoV555, uses a potent anti-spike neutralising monoclonal antibody that binds to the receptor-binding domain of SARS-CoV-2, (Jones et al., 2020). In a trial, involving outpatients with mild/moderate COVID-19, those who received a single intravenous infusion of neutralising antibody LY-CoV555, had less severe symptoms, reduced viral loads and a lower percentage of COVID-19–related hospitalisation compared with those who received placebo (Chen et al., 2021). Because, the monoclonal antibodies target different parts of the virus, it is possible that administering several together may produce a synergistic effect and may limit the emergence of neutralisation-escape mutants (Pinto et al., 2020; Roodink et al., 2021).

SARS-CoV-2 convalescent-derived antibodies used in clinical trials have given mixed results, whereas monoclonal antibodies demonstrated improvement in non-hospitalised patients, treated early in their illness.

4.4. Monoclonal antibodies and drugs in COVID-19 illness

Both IL-6 monoclonal antibody tocilizumab, or its receptor antibody have been prescribed widely in COVID-19 patient clinical care, though with mixed reports on patient hospitalisation and mortality (Salvarani et al., 2021; Stone et al., 2020; Wise, 2020). Two recent trials have added more information for tocilizumab. In the Randomised, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP), patients receiving an IL-6 receptor blocker had improved in-hospital mortality compared with the control group, whereas in the COVACTA randomised controlled trial, mortality at 28 days was not different in either groups (REMAP--CAP Investigators 2021; Rosas et al., 2021). Subgroup non-peer reviewed results in the RECOVERY trial indicated that those receiving glucocorticoids had a survival advantage, interpreted to suggest that glucocorticoid use in addition to tocilizumab, which was more standard in the later REMAP-CAP and RECOVERY trials, as compared to the COVACTA trial, could explain differing results (RECOVERY Collaborative Group, 2021a; Rubin et al., 2021).

Increased levels of pro-inflammatory cytokines IL-1α, IL-1β, IFN-α, IL-17A and IL-12p70 characterise a 'core' signature of severe COVID-19 illness, as compared with lower levels found in moderate illness. IL-1 and IL-1β inhibitors have been used clinically, though results have been mixed, suggesting that patient stratification and timing of use, may be important (Conti et al., 2020a,b; Cavalli and Dagna, 2021). IL-1 inhibition with anakinra in small studies produced rapid reduction of the systemic inflammatory response and improved oxygenation (Ucciferri et al., 2020; Huet et al., 2020), whereas canakinumab did not improve outcomes in patients with mild-to-moderate COVID-19 pneumonia (Aouba et al., 2020; The CORIMUNO-19 Collaborative Group, 2021). Other soluble receptor antagonists, chemokines, microRNAs-MiR-146 and MiR-125 (Lee et al., 2016), and siRNAs also function as inhibitors for pro-inflammatory cytokines and have potential for use in COVID-19 treatment.

Remdesivir is the main anti-viral agent that has demonstrated some benefit in treatment of COVID-19 patients, with faster time to clinical improvement than those receiving placebo, among patients with symptom duration of 10 days or less (Beigel et al., 2020; Wang et al., 2020b). A small Israeli phase 1 clinical trial has reported in the press that moderately ill COVID-19 patients were discharged in 3–5 days, when given a new substance EXO-CD24, containing a protein CD24, and delivered to the lungs by exosomes (Penna, 2020). CD24, expressed by many immune cells, helps rebuild and rebalance the immune system and prevent inflammatory overaction (Chen et al., 2009a; Liu et al., 2009). More clinical studies are urgently needed to assess any new anti-viral agents, anti-inflammatory cytokines or cytokine genotypes that could contribute to reducing the severity of the pro-inflammatory phenotype and 'cytokine storm' seen in seriously ill Covid-19 patients (Al-Beltagi et al., 2021; Cao et al., 2020b).

Dexamethasone, a corticosteroid used in a wide range of conditions for its anti-inflammatory and immunosuppressant effects is effective in COVID-19 and reduces the risk of death by approximately 25% in seriously ill patients at risk of, or requiring mechanical ventilation (RECOVERY Collaborative Group, 2021b; WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, 2020). The benefit effect of glucocorticoids seems to be highly dependent on careful selection of dose, timing and patient clinical status.

Dexamethasone been found to be effective in COVID-19, dependent on dose, timing and patient selection; IL-6 monoclonal antibody tocilizumab, or its receptor antibody and IL-1 inhibition have shown some benefits.

4.5. COVID-19 vaccination effectiveness in older people

Numerous studies have shown that vaccine efficacy decreases with age, a reduction that is driven by the age-related decline of innate and adaptive immune responses and characterised by a combination of inflamm-ageing and immunosenescence. This not only puts older people at risk from the SARS-COV-2 virus but also makes it more difficult to produce a vaccine that will provide adequate protection in the oldest age groups. There is heterogeneity in each person's immune system, marked out by sex, age, genetics, ethnicity, lifestyle, and immunobiography (Franceschi et al., 2017; Rea et al., 2018). Yet there is evidence that many older people get good protection from vaccines; for example, at the age 70 the pneumococcal vaccine has an efficacy of about 60% (Djennad et al., 2018) and the adjuvanted herpes zoster shingles vaccine demonstrated a 90% efficacy against shingles in people $>$ 70 years of age (Le et al., 2017; Lal et al., 2015). The influenza vaccine effectiveness varies from one season to the next, and in the UK is estimated by Public Health England (2018), to be between 30% and 60% for adults aged 18–65 years. The challenge has been to produce a COVID-19 vaccine that is safe, with the ability to produce an immune response that is sufficiently protective for people at every age of life.

A large number of vaccines against COVID-19 have been developed and are in use, based on different platforms such as lipid particles, mRNA, DNA, adjuvant proteins, inactivated virus particles and non-replicating viral particles. The BNT162b2 (Pfizer-BioNTech) vaccine began the first ever immunisation programme against the SARS-COV-2 virus in December 2020, $<$ 12 months after SARS-CoV-2 was identified. The vaccine is novel and uses a piece of messenger mRNA from the SARS-CoV-2 spike protein combined with a lipid nanoparticle, to stimulate production of antibodies against the mRNA fingerprint of the SARS-CoV-2 virus. The results showed that the Pfizer vaccine worked with an efficacy of 95% overall, including for older participants (Polack et al., 2020). The Moderna (mRNA-1273) vaccine uses similar mRNA biotechnology (Baden et al., 2021; Anderson et al., 2020) and shows vaccine efficacy of 86% for participants, 71 years or older (Widge et al., 2021). The Moderna and the Pfizer vaccines have documented detecting neutralising antibodies and significant CD4 cytokine Type-1T helper cell responses within several weeks (Polack et al., 2020; Widge et al., 2021), but it has yet to be established that the immune response and antibodies will confer long-lasting, adequate immunity to COVID-19, particularly in those in the $>$ 70s, and those in immunosuppressed 'at risk' groups (Anderson et al., 2020; Walsh et al., 2020).

The adenovirus-vector-based vaccine ChAdOx1 nCoV-19 (AZD1222) (Oxford–AstraZeneca), produced by Oxford Vaccine Group, demonstrated good anti-spike SARS-CoV-2 IgG responses and neutralising antibody titres after a booster dose in both older ($>$70 years) and young participants (Folegetti et al., 2020; Ramasamy et al., 2020). Overall vaccine efficacy across groups was 70·4%, and an increased 12-week gap between vaccines, improved efficacy (Voysey et al., 2021). However, only 3% of participants were in the $>$ 70s-age-group, and additional confirmation in older people with co-morbidities would be highly valuable (Knoll and Wonodi, 2021).

Both Pfizer and AstraZeneca vaccines produce strong immunogenicity and high short-term efficacy, but antibodies wane over time (Shrotri et al., 2021). However, research is confirming the longer-term presence of SARS-COV-2 memory cells in patients recovered from COVID-19 (Wheatley et al., 2021; Gaebler et al., 2021; Rodda et al., 2021; Doria-Rose et al., 2021), which strongly suggests that immune responses could develop on SARS-CoV-2 re-exposure; the findings are further validated from research demonstrating that vaccination reduces serious illness, hospitalisation and death after COVID-19 re-infection (Amit et al., 2021; Dagan et al., 2021; Vasileiou et al., 2021; Lumley et al., 2021). The emerging reports of breakthrough infections in healthcare workers (Bergwerk et al., 2021), and the surge in cases caused by the Delta-variant have caused countries to look more closely at booster vaccinations; these will likely be required to maintain adequate longer-lasting immunity, particularly in the $>$ 50s age-group and for those in an immunosuppressed 'at risk' group (Callaway, 2021).

Other vaccines have been developed – Sinovac in China and Sputnik in Russia, with thousands of participants being vaccinated. The Sputnik

V Phases 1/2 and 3 trials, using a combination of 2 adenovirus-based vaccines, reported fairly good efficacy and safety, and adequate but lower IgG spike and neutralising titres in participants > 60 years of age (Logunov et al., 2020, 2021). The Johnson/ Johnson/Janssen Ad26COV2 S vaccine, a single shot, normal temp-based, DNA vaccine, has presented data demonstrating good early efficacy, with production of neutralising antibodies against the spike protein with CD4+ T helper Th1 and Th2 cells, present in participants aged 18–65 years (Sandoff et al., 2021).

The rapid spread of the new SARS-CoV-2 variants is concerning, and more mutations are likely to arise. Vaccine teams are keen to reassure the public and politicians that the newly developed vaccines will be able to curb the virus, irrespective of the variants (Callaway, 2021), and that vaccine manufacturing will cover new variant combinations (Xie et al., 2021b). To date virtually all other variants have been driven off by the far more transmissible B.1.617.2 Delta-variant of SARS-CoV-2, which is spreading rapidly across the world. The efficacy of current vaccines against the Delta-variant is moderately good at preventing serious illness, hospitalisation and death, but its high transmissibility is of concern. However, despite reassurances, there is a clear risk that future epidemic waves may be larger, producing a greater burden of transmission, infection, serious illness and death globally. Prospective mapping of mutations during viral surveillance, may enable prediction of the consequences of mutations and allow proactive, prospective vaccine development (Starr et al., 2021).

There is very good early efficacy from new RNA and DNA-related COVID-19 vaccines, but antibody levels wane with time, and boosters will likely be needed in older groups and those in immunosuppressed 'at risk' groups.

4.6. *Controlling inflamm-ageing: a possible treatment approach for COVID-19 in older individuals (456)*

Inflamm-ageing, (Franceschi et al., 2000) contributes to many age-related diseases (Fig. 10) (new inflamm-ageing), and is associated with global indicators of poor health status, multimorbidity, and premature death, all factors that increase risk of serious illness from COVID-19 illness. Age-related diseases such as cardiovascular disease, hypertension and diabetes continue to be treated by clinical guidelines and drugs such as anti-hypertensives, aspirin, statins and metformin, during COVID-19, to maximise treatment of patient co-morbidities. However, inflamm-ageing related to cardiovascular disease, diabetes and a range of cancers can be modulated not only by conventional drugs and behaviour change, but by targeting cellular inflammatory pathways, to improve or modulate inflamm-ageing (Ridker et al., 2021; Christoffersen and Tybjaerg-Hansen, 2021; Ferruci et al., 2018; Ruparelia et al., 2017). Several potential mechanisms that might contribute to inflamm-ageing, include genetic susceptibility, central obesity, increased gut permeability, changes to microbiota composition, cellular senescence and SASP, NLRP3 inflammasome activation, oxidative stress, dysfunctional mitochondria, DNA damage and immune cell dysregulation (López-Otín et al., 2013; Kennedy et al., 2014), and researchers are developing re-purposed drugs to improve understanding of cellular signalling pathways involved.

4.6.1. *Metformin*

Central obesity is strongly associated with a pro-inflammatory state and inflamm-ageing (Frasca et al., 2017). Metformin used in type 2 diabetes and obesity help with weight control and appetite (Sanchez-Rangel and Inzucchi, 2017), and acts at the molecular level to damp down inflamm-ageing, regulate the mitochondria and inflammasome (Barra et al., 2020), and reduce activation of the NF-κB signalling pathways. Diabetes increases risk for serious illness and death from COVID-19 (Apicella et al., 2020) and outcomes have been improved by metformin treatment (Dardano and Del Prato, 2021; Sharma et al., 2020). In a retrospective cohort analysis of hospitalised patients with obesity or type 2 diabetes presenting with COVID-19, prior metformin use, reduced mortality by 25%, but more in women compared to men (Bramante et al., 2020). Further trials are planned.

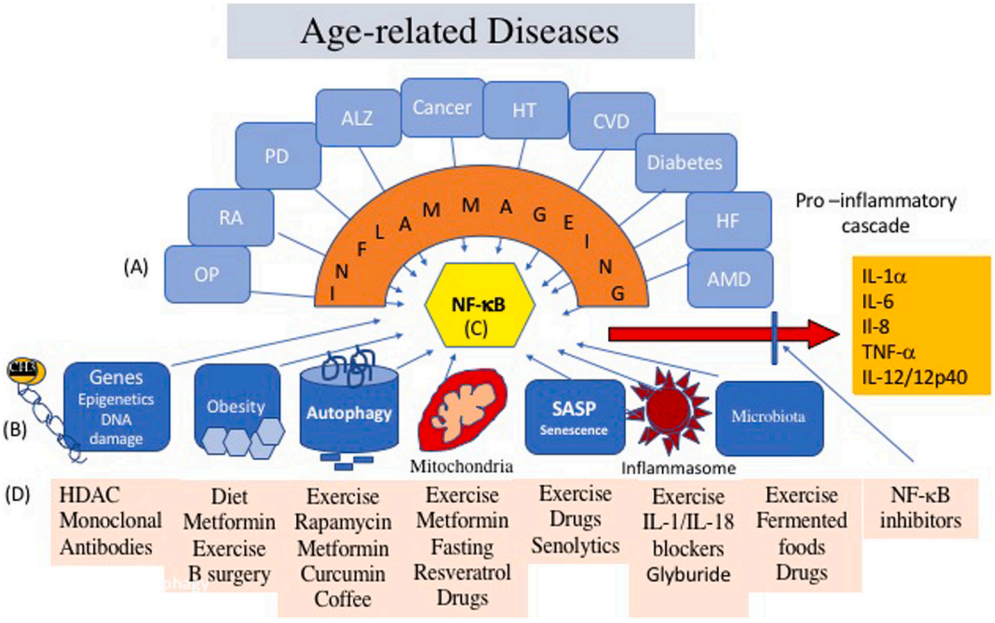

Fig. 10. Controlling Inflamm-ageing: a possible treatment approach for COVID-19 in older people. Multiple age-related diseases occur with increasing age. (A) Inflamm-ageing contributes to many age-related diseases for example, atherosclerosis, rheumatoid arthritis, diabetes and Alzheimer's Disease, and is associated with poor health status. (B) Several potential mechanisms that might contribute to inflamm-ageing include genetic susceptibility, central obesity, reduced autophagy, mitochondrial dysfunction, cellular senescence and SASP, inflammasome NLRP3 activation, changes to microbiota, oxidative stress, DNA damage. (C) The signalling pathways that link age-related diseases and inflamm-ageing join a common downstream signalling pathway causing NF-κB to translocate into the nucleus and resulting in activation of a low grade pro-inflammatory cytokine-related, sterile inflammation. (D) Researchers are developing re-purposed drugs and new molecules to improve understanding of the cellular pathways involved in inflamm-ageing. Evidence is becoming available as to how conventional drugs such as metformin used in diabetes and behaviour changes such as exercise, diet or episodic fasting, together with monoclonal antibodies, can be shown to reduce inflamm-ageing and improve disease management. OP, osteoporosis, RA, rheumatoid arthritis, PD, Parkinsons Disease, Alz, Alzheimers Disease, HT, hypertension, CVD, cardiovascular disease, HF, heart failure, AMD, age-related macular degeneration, HDACs, histone deacetylases, B-surgery, bariatric surgery.

4.6.2. Rapamycin

Cellular senescence increases in multiple human tissues and cells with age (Gillispie et al., 2021; Rossman et al., 2017). As senescent cells accumulate, SASP develops secreting interleukins, chemokines, growth factors and metalloproteinases, that spread cellular senescence in neighbouring cells, and activate NF-κB signalling. Inhibition of the mechanistic target of rapamycin complex 1 (mTORC1) with rapamycin, has been shown to delay or reverse many age-related phenotypes, including declining immune function (Chen et al., 2009b; Baker et al., 2011, 2016). Natural senolytics are present in foods such as resveratrol in grapes, quercetin in onion and catechins in tea.

There have been calls for small doses of rapamycin to be used in the treatment of COVID-19, based on evidence from studies showing rejuvenation of the immune system and improved response to influenza vaccination (Bischof et al., 2021).

5. Final comments

In the new global reality of living with Covid-19 there are many unanswered questions. The new type of RNA vaccines produced by Pfizer and Moderna, Novavax and the more traditional vaccines of Oxford/Zeneca and Johnston/Janssen have produced good initial antibody results in older people but as with previous knowledge about other vaccinations, immunoprotection begins to wane early, fitting with the well-recognised weaker immune responsiveness in the oldest and frailest people (Andrew et al., 2020; McElhaney et al., 2020; Aspinall and Lang, 2018). Already, Israel, a country with high population vaccination rates has completed a third dose vaccination programme, to people as young as 50 years of age (Mizrahi et al., 2021: Wadman, 2021). A population-level study from Denmark estimated that protection against re-infection with SARS-CoV-2 fell by half in older people, compared to younger people (Hansen et al., 2021). Like the 4 other common coronaviruses in population circulation, seasonal re-exposure and re-infection seem likely to be required, to maintain immunity (Monto et al., 2020). Currently, booster doses are being considered at 12 months or earlier and given with the influenza winter inoculation. Mixing and matching two or even three vaccines, rotating primer and booster doses, adding adjuvant/s or increasing antigen dose, to improve efficacy in older aged groups, are being considered, and some are undergoing testing.

Despite the best efforts of governments, scientists and clinicians, some people will decline or be unable to be vaccinated and that includes health care staff, caring for the oldest and frailest people. Non-uptake of vaccine risks reduces population and global immunity and undermines the hope of ending the COVID-19 pandemic across the world. The unequal supply and sharing of vaccines, puts all countries at risk and could contribute to the further emergence of mutations. Successful population vaccination helps countries move towards herd immunity, but even without herd immunity, vaccination of vulnerable people seems to have reduced hospitalisations and deaths from COVID-19. Continuing with behavioural and non-pharmaceutical interventions are likely to be necessary to keep COVID-19 case numbers down, with high transmissibility of the Delta variant or any new antigenic evolution. Increased understanding of the immunology of COVID-19 illness in the older person has never been more important, and the opportunity never greater, to progress immunological knowledge and skills that are likely to benefit everyone irrespective of age. COVID-19 seems unlikely to disappear any time soon; it can only be hoped that its prominence might begin to wane with better targeted vaccines, and an improved focus on rapid equitable vaccine distribution for global control of the pandemic.

Ethical issues

There are no ethical issues.

Author contributions

Both HDA and IMR conceived and designed the outline of the manuscript and both authors contributed to the drafting and revising of the manuscript and its various iterations prior to approving the manuscript prior to submission.

Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be considered as a potential conflict of interest.

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