The impact of inflammageing on SARS-Cov-2 infection

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Summary

Baseline inflammation increases during ageing and inhibits immunity. Strategies to block inflammation may benefit immunity in older SARS-Cov-2 infected patients.

Ageing is associated with increased morbidity arising from a wide range of tissue dysfunction. A common denominator associated with age associated frailty is the elevated baseline inflammation, called inflammaging, that is present in older individuals. Recent studies have shown that the presence of excessive levels of inflammation can inhibit immunity in both animals and humans and that this can be prevented blocking the inflammatory processes. This has important implications for the immunity of older individuals who are infected with pathogens such as SARS-Cov-2 that induce overwhelming inflammation. Here we discuss the impact of inflammageing on immunity in healthy and address the possibility that reducing inflammation may be a therapeutic strategy for enhancing immunity to this virus *in vivo*.

A novel Coronavirus (SARS-CoV-2) that causes severe respiratory disease (COVID-19) emerged from Wuhan in China in December 2019. The World Health Organisation (WHO) declared the global spread of the virus as a pandemic. While COVID-19 infection only induces mild to moderate symptoms in younger individuals, the viruses induces devastating morbidity and mortality in older subjects and a key hallmark of severe disease is exuberant inflammation that in the respiratory tract of patients (*1*).This raises the question of where this inflammation originates from and whether effective anti-viral immunity can be initiated in this inflammatory environment.

Older healthy individuals exhibit chronic low-grade sterile inflammation characterised by high baseline levels of serum concentrations of C Reactive protein (CRP) and cytokines including interleukin (IL)-6, IL-8 and TNFα, a phenomenon known as inflammageing, that predicts frailty and earlier mortality(*2*). This elevated inflammation may arise as a result of multiple

mechanisms including the accumulation of misfolded proteins, compromised gut barrier function and also obesity(*2*). Furthermore, defective resolution of an immune responses in older individuals may also lead to sustained inflammation *in vivo* (*3*). Senescent cells, that accumulate in every organ of older individuals, may also contribute to inflammageing(*4*) Senescent populations are found within diverse cell lineages and are non-proliferative as a result of telomere erosion, damaged DNA, epigenomic changes or mitochondrial dysfunction (*5*). However these cells can secrete inflammatory cytokines, chemokines, growth factors and matrix metalloproteinases (MMPs)(*5*). This is known as the senescence associated secretory phenotype (SASP) and the spontaneous secretion of these molecules and may cause tissue inflammation in the absence of any stimulus leading to organ dysfunction(*5*).

Inflammation is an essential component of the initiation phase of an immune response and is actively reduced during immune resolution to enable the restoration of tissue homeostasis. However, the presence of excessive inflammation can inhibit immunity *in vivo*. This is illustrated by studies showing that elevated inflammation is detrimental for the efficacy of many vaccines e.g. against influenza(*6*). However the negative impact of inflammation on immunity during ageing can be reversed in part by treatment with the mTOR inhibitor Rapamycin, that enhances vaccine response to influenza in older humans(*7*). Furthermore, the short-term administration of an oral p38 mitogen-activated protein (MAP) kinase inhibitor was shown to reduce baseline cutaneous inflammation of older humans that resulted in significantly increased response to VZV recall antigen challenge *in vivo*(*8*). Therefore, reducing inflammageing with a short-term course of anti-inflammatory drugs may be a strategy for immune enhancement in older humans. This may be of particular relevance for older patients with COVID-19 who have severe inflammation in the respiratory tract that may hinder anti-viral immunity.

Both senescent cell numbers and baseline inflammation increase during ageing suggesting the possibility that both of these events are interlinked. Since senescent cells secrete pro-inflammatory mediators and accumulate in every organ in the body during ageing, another way to enhance immunity may be to eliminate these cells that would reduce the inflammatory burden. Natural mechanisms exist for clearing senescent cells from tissues that involve the expression of “kill me signals” on senescent cell populations that activate receptors on cytotoxic lymphocytes(*9*). The ability of leukocytes to eliminate senescent cells begs the question of why these cells accumulate during ageing. One possibility is that the general multifactorial age associated decline in immunity also extends to senescent cell

surveillance. Alternatively, senescent cells may display evasion strategies that enable them to escape from immune clearance. These mechanisms include the shedding of decoy receptors that interfere with the ability of cytotoxic cells to recognize them(*10*) and also the expression of inhibitory “don’t kill me” signals on their cell surface(*9*). The removal of senescent cells in mice can reverse age-associated organ dysfunction consequently, therapies to remove senescent cells with drugs termed senolytics are currently being developed and tested in both mice and humans(*11*).

Therefore, blocking inflammation directly or eliminating the cells that produce these mediators can improve both health and immunity. The presence and inflammatory nature of senescent cells in various tissues may inhibit immune responses of older individuals and this has to be factored in when considering the cause of the massive inflammatory responses during certain infections e.g. SARS-Cov-2. Since senescent cells increase in the lungs during ageing(*12*), they are very likely to be present in the lungs of older COVID-19 patients and may participate in the initiation of an inflammatory cascade. Although the secretion of pro-inflammatory mediators by adipose tissue may contribute to inflammageing it is not yet known if senescent cells in the adipose tissue or the adipocytes themselves produce these mediators. This is relevant in the context of COVID-19 as obesity is one of the co-morbidities for severe disease.

A key unknown is the relationship between high baseline inflammation and the massive inflammation that occurs in older COVID-19 patients with severe disease. One hypothesis is that pre-existing inflammatory cells including senescent populations and adipocytes create the inflammageing phenotype that is the trigger for subsequent inflammatory events. This would involve the recruitment of other inflammatory cells such as monocytes from the circulation(*13*). Nevertheless, high levels of inflammation alone does not explain the devastating tissue destruction that is observed in the lungs of COVID-19 patients with severe disease and it may be that age-associated changes in T cells may have a role in the immunopathology. T lymphocytes that have differentiated towards an end-stage accumulate in older subjects and they lose the capacity to proliferate after activation but are highly efficient cytotoxic cells(*14*). The caveat to this is that the same cells now express natural killer receptors (NKR) and can kill different cell types that express NKR ligands (*14*). Inflammation has been shown to increase the expression of NKR-ligands by different cell types(*15*). Therefore, T cells that infiltrate the lungs of COVID-19 patients may not work well in an antigen-specific manner because of the inflammation present but also because they

now behave more like NK cells. This NK cytotoxic activity of infiltrating T cells may contribute to the reported collateral tissue damage in the respiratory tract of COVID-19 patients. Consequently, there is an urgent need for immunohistological data from the lungs of these patients to address this possibility.

As discussed, the excessive inflammation that occurs during an immune response in older individuals may not be produced by a single cell type but may instead arise from a cascade of cellular interactions. Senescent cells in tissues of old COVID-19 patients would recruit inflammatory monocytes into the tissue from the circulation and these monocytes amplify the inflammation that is observed*(13)*. There appears to be a counterpart for this in the lungs of COVID-19 patients where there is massive infiltration by inflammatory monocytes(*16*).

The propensity to mount inflammatory responses in tissues and changes in the behaviour of different leukocyte populations have to be taken into consideration when addressing the immune responses of older subjects during infection. The baseline inflammation may not be detrimental in itself, instead it may initiate an inflammatory cascade that amplifies the response. In addition to senescent cells other cell types that are inflammatory such as adipocytes may also be the initial trigger for inflammation. Inflammageing has many implications for COVID-19 patients. The accumulation of senescent cells in the respiratory tract of older patients may be involved in the initiation of an inflammatory cascade that would inhibit T cells responses to virally infected cells that are present. Another consequence of the inflammation would be the induction of NKR ligand expression by cells in the lung(*15*) that would make them susceptible to killing by infiltrating T cells that express NKR. The search for an effective vaccine for COVID-19 has also to consider the decreased vaccination efficacy in older subjects that may be associated with inflammageing(*17*). Therefore the effective treatment COVID-19 patients may require a combination of anti-inflammatory, anti-viral regimes to compliment vaccination against the virus.

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