CORONAVIRUS

Targeting aging cells improves survival

Drugs that remove senescent cells cut coronavirus deaths in old mice

By Lynne S. Cox and Janet M. Lord

Older age is associated with increased COVID-19 severity and mortality (1). Whether this is due to preexisting age-related health conditions or aging per se is currently unclear. On page 295 of this issue, Camell et al. (2) show that cell senescence, a hallmark of biological aging (3), contributes to mortality in old mice upon infection with mouse hepatitis virus (MHV), a mouse β-coronavirus that is similar to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Mirroring findings from human COVID-19, they show that old—but not young—mice infected with MHV succumb rapidly to viral infection. They demonstrate that treatments to remove senescent cells (senolytics) significantly improve survival in older mice, even when initiated 3 days after infection. These findings provide a biological explanation for the effect of age on COVID-19 severity and strongly support the testing of drugs that target senescence in older patients with SARS-CoV-2 infection.

Senescence is a tumor-suppressive, non-proliferative state induced by chronic cellular stress or damage, and senescent cells accumulate with increasing age. Cell senescence has been suggested to be a major biological driver of age-related dysfunction and morbidity as well as further exacerbating disease states such as diabetes and atherosclerosis (4). These pro-aging effects are due in large part to a complex secretome that contains inflammatory cytokines and chemokines, angiogenic growth factors, and tissue-remodeling metalloproteases, collectively known as the senescence-associated secretory phenotype (SASP) (5). Although beneficial under acute stress or injury, the persistent SASP that occurs as a result of senescent cell accumulation in older adults leads to chronic inflammation (6). This “inflamming” may be pathogenic for multiple age-related diseases. Transplantation of senescent cells into young mice induces a broad range of age-related

**Cellular senescence amplifies damaging inflammation**

Senescent cells secrete inflammatory mediators and proteases, which contribute to age-related disease. Upon coronavirus infection, senescent cell load and the secretome increase, which drives inflammation, tissue damage, further infection, inflammation-related pathology, and death. Removal of senescent cells with senolytic drugs reduces inflammation to below the “young” threshold, allowing disease resolution and survival.

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**REFERENCES AND NOTES**

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diseases (7), whereas their removal from old mice improves health across multiple organ systems and increases life span (8).

Why might senescent cells be detrimental in infectious diseases such as COVID-19? Camell et al. show that in vitro exposure of senescent human cells to pathogen-associated lipopolysaccharide (LPS) and the S1 subunit of the SARS-CoV-2 spike protein (which mediates cell entry) leads to increased expression of senescence markers and the SASP. Similarly, MHV-infected old (but not young) mice exhibit increased cell senescence and SASP factors, suggesting that pathogen exposure can amplify detrimental inflammation because of senescent cells (see the figure). These findings extend our understanding of the role of viral infection in driving formation of SASP-producing senescent cells (9). Notably, SASP factors—especially interleukin-1α (IL-1α)—were found to reduce the expression of interferon-induced transmembrane proteins (IFITMs), a first-line of antiviral defense, as well as increase the expression of the SARS-CoV-2 entry receptor angiotensin-converting enzyme 2 (ACE2) and co-receptor transmembrane protease serine 2 (TMPRSS2) in nonsenescent cells. Hence, SASP secretion predisposes adjacent cells to higher viral infection and poorer innate antiviral responses, in addition to increasing inflammation and tissue damage.

It can be deduced from these findings that the higher the senescent cell burden, the more likely SARS-CoV-2 infection is to lead to severe COVID-19. Older adults (>70 years) and those with chronic conditions such as obesity and diabetes, who already have high amounts of senescent cells and high levels of inflammation (10), are most at risk of poor COVID-19 outcomes. The extra “push” from infection is likely to both increase the senescent cell burden and drive senescent cells over a threshold into highly damaging inflammation. Key SASP factors are also those most associated with the lethal cytokine storm that occurs in severe COVID-19 (2). Such inflammation is likely to activate complement and clotting cascades, potentially contributing to the high incidence of thrombotic events in severe COVID-19 (11) as well as resulting in excess recruitment of neutrophils and natural killer (NK) cells to the lungs, leading to acute respiratory distress syndrome (ARDs).

To test whether senescent cells contribute directly to coronavirus mortality, Camell et al. removed senescent cells from infected mice by inducing apoptosis through senescence-specific caspase expression or by treating with senolytic drugs fisetin or a combination of dasatinib and quercetin (D+Q). All approaches resulted in greatly enhanced survival compared with controls. The treatments were accompanied by decreased expression of senescence and SASP markers. Moreover, treated survivors showed improved coronavirus antibody responses; this may simply be because mice survived long enough to mount a full adaptive immune response but may also reflect partial rejuvenation of the immune system through the removal of senescent immune cells.

Senolytic drugs have considerable promise for treating human COVID-19 patients, especially older adults. Fisetin is now in clinical trials in clinically vulnerable adults with COVID-19 (NCT04476953). Moreover, senolytic therapy may also have potential beyond the acute infection phase. Improved physical function has already been reported in patients with idiopathic lung fibrosis, a serious condition with high senescent cell load, after short-term senolytic D+Q treatment (12). Therefore, “long COVID” patients suffering from lung fibrosis and difficulty breathing may benefit from senolytic therapy.

In addition to senolytics, other drugs that modify senescent cell behavior may be useful in COVID-19 prophylaxis and treatment (13). Inhibitors of mammalian target of rapamycin (mTOR) can act as pleiotropic “geroprotectors,” suppressing senescence and the SASP, enhancing antiviral gene expression, and improving adaptive immune responses (14). At the low doses that confer geroprotection, mTOR inhibitors are well tolerated in older adults (age 65 to 85 years)—including those with diabetes, asthma, and cardiovascular disease (15).

Even with highly effective vaccination campaigns, COVID-19 is likely to become endemic, posing particular dangers to vulnerable older people and those with underlying health conditions. The findings of Camell et al. strongly support clinical trials of treatments that target senescent cells in COVID-19 patients, as well as in care homes and long COVID clinics, to improve both resistance to infectious disease and recovery from COVID-19, which if unchecked will contribute to poor quality of life and persistent ill health of COVID-19 survivors. ■

REFERENCES AND NOTES

Nudging germ cell precursors into functionally mature oocytes and spermatozoa is a key aspect of in vitro gametogenesis and a major challenge in the study of reproductive biology. This process is biologically complex, not only determined by the developmental competency of the germ cell itself but also critically dependent on the gonadal niche. On page 298 of this issue, Yoshino et al. (1) report the in vitro derivation of fetal ovarian somatic cell–like cells (POSCLCs) from murine pluripotent embryonic stem cells, using a stepwise, directed differentiation strategy to reconstruct in vivo differentiation. These cells sufficiently supported the development of germ cell precursors into functional oocytes that went on to produce viable, fertile mice. The ability to generate and assemble the critical components necessary for oogenesis in the laboratory provides a model system to study the later events of oogenesis, and this may have implications for assisted reproductive technologies.

The preceding decade saw great strides made in understanding early developmental processes in gametogenesis. In the laboratory, methods to direct the specialization of pluripotent stem cells—a renewable cell source—to primordial germ cell–like cells (PGCLCs) from murine pluripotent embryonic stem cells, using a stepwise, directed differentiation strategy to reconstruct in vivo and producing functional germ cell entirely ex vivo.

Further development of mammalian primordial germ cells occurs with their migration to the genital ridges (the location where gonads develop in both sexes) (5). In mam-
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