Cellular senescence and COVID-19: Benefits of the formula MISEN

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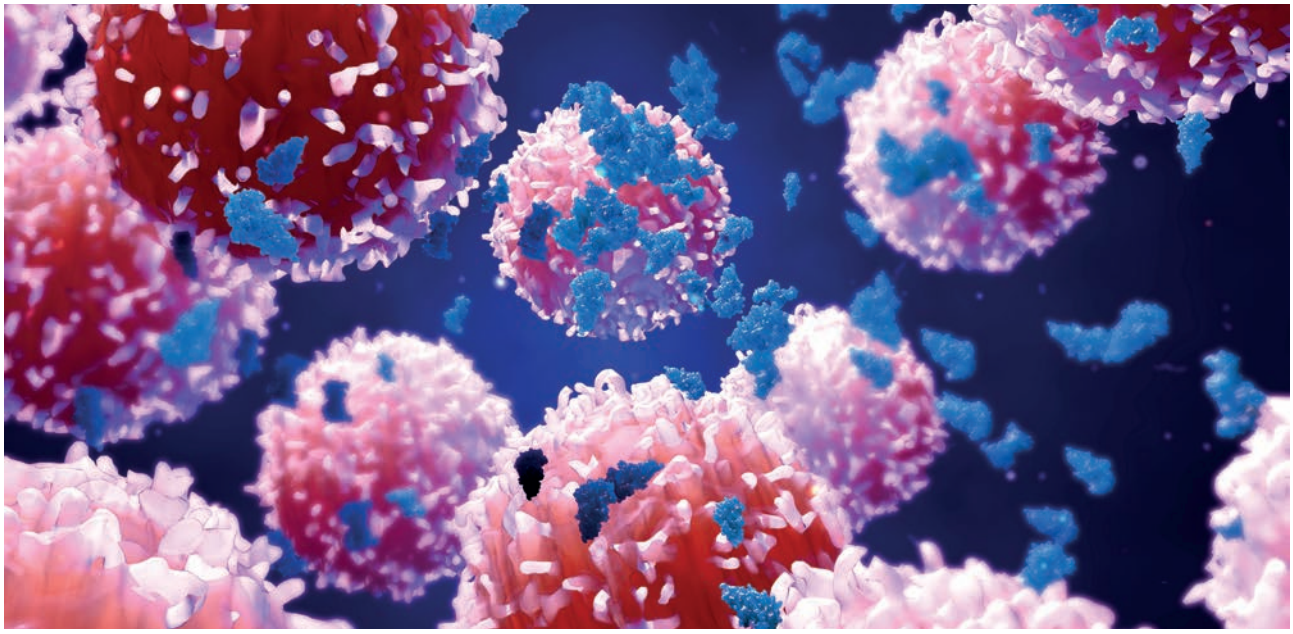


Cellular senescence is a response mechanism to stress-induced modifications such as telomere shortening, DNA damage or mutations that leads to a permanent arrest of the cell cycle[1]. Although senescence and apoptosis are critical processes to ensure tissue function[2], chronic accumulation of senescent cells can block tissue repair and regeneration, thus contributing to tissue ageing[3].

Recent reports are revealing increased expression of senescence markers and T cell exhaustion in patients with a past COVID-19 infection, sustained for months after the onset of symptoms[4-9]. These factors may play an important role in subsequent complications associated with the infection[10].

Implications of cellular senescence

Ageing and its association with cellular senescence are now recognised as one of the main risk factors for the development of chronic diseases such as cancer or cardiovascular disease[8]. Accumulation of senescent cells has also been observed in pathologies like diabetes, neurodegeneration, fibrosis, osteoporosis or obesity[1,11-16].

Cellular senescence is a stable and usually irreversible cell cycle arrest, characterised by alterations in cell morphology and metabolism as well as the development of a potent proinflammatory secretory environment: the senescence-associated secretory phenotype (SASP), characterised by the secretion of different inflammatory cytokines, chemokines (TNF-α, IL-1, IL-6, IL-8) and proteases. In senescent cells, a number of characteristic changes occur: arrest of the cell cycle, increased expression of antiproliferative molecules such as $p16^{INK4a}$, promotion of caspase activation-asso-

ciated apoptosis, as well as induction of cell damage-associated signalling pathways like $p38^{MAPK}$ and NF-κB.

There are various types of senescence, from physiological (associated with processes like wound healing, tissue remodeling or antitumor protection), replicative (associated with telomere shortening), stress-induced (caused by oncogene activation, metabolic stress, oxidative stress, inflammatory cytokines or cell damage) to therapy-induced senescence[8].

Just like programmed cell death, cellular senescence is a strictly controlled process in the organism. A diminished capacity of the immune system to eliminate senescent cells can lead to an increase and accumulation of altered cells. Moreover, chronic inflammation due to SASP can reduce the immune system's capacity to control and eliminate senescent cells. A good strategy to attack senescent cells is to strengthen the immune system so it detects and eliminates these cells efficiently, a process known as immune surveillance[17].

Immunosenescence: Ageing of the immune system

Paradoxically, immunosenescence, i.e. the ageing of the immune system, results in a reduced capacity to control senescent cells. Although cellular senescence and immunosenescence are very similar processes, they refer to different cell populations, the former including the latter.

Immunosenescence affects both innate and adaptive immunity. For example, the accumulation of senescent macrophages can be related to ageing itself and the influence of their microenvironment; in this particular case it seems to be more related to a phenotypic change. In general, a decrease in M1 proinflammatory macrophages and an increase in M2 macrophages has been observed in immunosenescence, which may be associated with reduced capacity to eliminate viruses and senescent cells. In NK cells, ageing is particularly associated with functional changes such as reduced cytotoxic capacity or modifications in surface molecules[18]. As regards adaptive immunity, reduced diversity of T cell receptor (TCR) repertoire, accumulation of exhausted cells and memory cells have been observed in ageing. Also, regulatory phenotypes increase, whereas cytotoxic TCD8+ and antibody secretion by plasma cells decreases[19]. Changes occurring in lymphocytes include a drop in co-stimulatory molecules like CD28 both in CD4+ and CD8+ T cells, which are necessary for the activation and proliferation of these cells at multiple levels, as they mediate the progression from the G0 to the G1 phase[20]. CD28 null cells participate in various inappropriate responses that contribute to a dual inflammatory and immunosuppressive state. Besides being senescent, both CD4+ and CD8+ CD28 null cells are resistant to apoptosis, resulting in the accumulation of these cells in chronic diseases such as cancer, hypertension, diabetes, EPOC or chronic viral infections[21-26].

Overall, changes associated with immunosenescence lead to increased susceptibility to age-associated pathologies given the reduction in the defence capacity against pathogens, accumulation of senescent cells and the promotion of a chronic inflammatory environment.

SARS-CoV-2 and cellular senescence

It is known that cellular senescence can be induced by viruses (VIS) as well, either as an antiviral defence mechanism in response to pathogens or as a response to antiviral treatments[27,28]. Some viruses, however, exploit the senescence programme for their own benefit to improve replication[27].

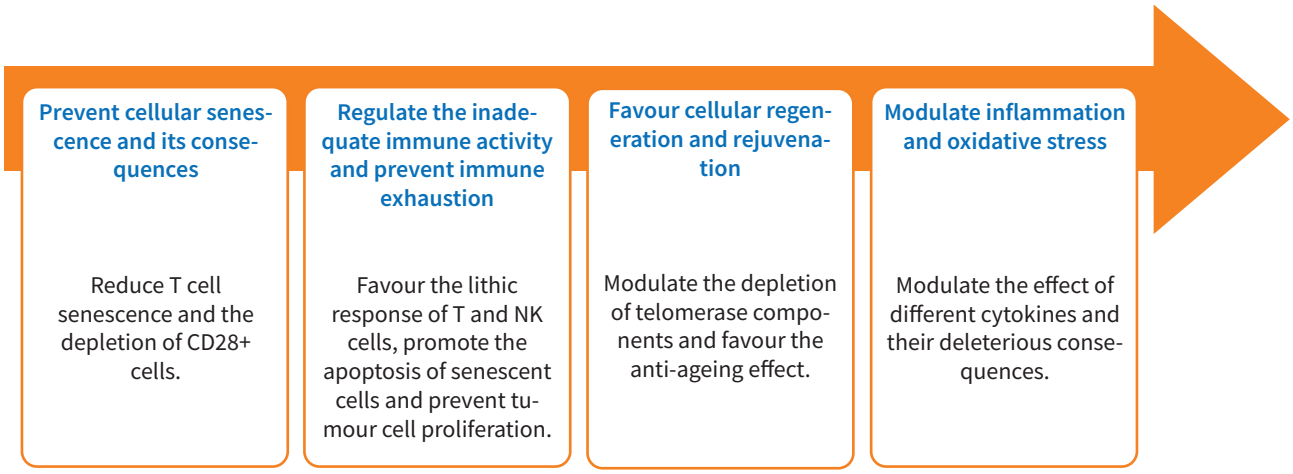
The mechanisms of pathogen-induced senescence have been described for various pathogens such as the Epstein-Barr virus (EBV) or the cytomegalovirus (CMV), as well as senescence inhibition processes associated with other viruses such as the human papillomavirus or EBV[29]. Senescence can be directly or indirectly mediated by a pathogen, namely through an increase of interferon levels by infected cells or the release of danger-associated molecular patterns (DAMPs) by cells undergoing cell death[8]. In addition, in virus-induced senescence the capacity of senescent cells to harbour viruses for longer periods of time increases the probability of the host editing the viral genome and inducing mutagenesis[30].

Although age is one of the main risk factors in COVID-19, little is known about senescence in relation to this disease. However, various studies suggest that senescence and ageing together play a central role in the pathogenesis of COVID-19. The fact is that multiple conditions linked to cellular senescence share the same characteristics as the complications associated with COVID-19 sequelae, including an increase in oxidative stress and mitochondrial dysfunction[18]. Some studies directly point to cellular senescence as a therapeutic target in SARS-CoV-2 infection, since it is suggested that the cytokine storm and tissue damage may be driven by virus-induced senescence. The same study revealed precisely the presence of senescence markers in the upper airway mucosa as well as high concentration of SASP factors in COVID-19 patients[7,31]. As early as 2020, other research was pointing to the presence of an immunosenescent phenotype associated with increased levels of inflammatory parameters and neutrophil-to-lymphocyte ratio (NLR)[32-33]. Also, more recent studies have shown that severe patients exhibit elevated levels of plasma cytokines together with T cell depletion (particularly CD4+ and CD8+), neutrophil accumulation, thrombocytopenia, high ferritin level and an increase in other inflammatory markers[18]. Moreover, some authors have reported about a reduction in the NK cell count and exhausted phenotypes in COVID-19 patients[34].

T cell exhaustion may also play an important role in the subsequent stages of the disease. In fact, various accounts have shown that the recovery time in COVID-19 can be long and is characterised by a dysregulation of the adaptive immunity at the level of specific TCD4+ and TCD8+ cells, which express exhaustion markers for months after the onset of symptoms. In fact, it has been observed that COVID-19 patients have a greater number of CD28 null senescent/exhausted T cells both in the CD4+ and CD8+ subsets, and that these worsen the prognosis of chronic disorders, promoting the development of consequences associated with COVID-19 and contributing to the impairment of protective immunity and the increase in pathogenic inflammation[5,9,36-41].

Micro-immunotherapy in the prevention of COVID-19-induced immunosenescence

Micro-immunotherapy formulas are compounds composed of various immunoregulatory active ingredients, each of which is aimed at different objectives directed at exerting an action on the overall system. Due to the composition and immunoregulatory objectives of the formula MISEN, as well as the extensive experience gained with this formula in chronic stress-derived immune exhaustion and as a basic immune support in elderly patients, it is of interest as part of the treatment of SARS-CoV-2 infections. It provides immunomodulatory support to manage the presence of senescent cells both in the acute infection and in patients with Long COVID. A summary of the immunoregulatory objectives of the formula MISEN in the context of COVID-19 is presented below:



Based on the practice and clinical experience of doctors of the international associations of micro-immunotherapy, the formula MISEN can be used to support immune function according to the following dosage:

Formula MISEN

1 capsule/day, 3 - 6 months.

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