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Review Article

Do Pathogenic Chronic Infections Cause Host Senescence?

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Aging and senescence are words used as synonyms, and refer to the progressive and deleterious changes that occur in cells, tissues and organs, which alter their functionality [1]. In complex multicellular organisms such as animals, aging begins as soon as embryonic development reaches its maximum stage of differentiation. Aging cannot solely be explained by telomere shortening optics, but rather a combination of factors,including protein assembly and packaging errors, somatic mutations and errors in DNA repair, free radicals, reactive oxygen species, and epigenetic modifications such as hypermethylation [2]. Through molecular control, cells in their maximum state of differentiation stop dividing or reduce their cell division rates. Even tissues of intense proliferation accumulate mutagenic events, whether by environmental factors, by pathogenic infection, or by the events described above that stimulate senescence. Physiologically, our body uses strategies to eliminate senescent cells, damaged cells, or are able to recycle malformed organelles or proteins without the need for cellular elimination. Through autophagy or the removal of senescent cells by the immune system, our body prevents the accumulation of these cells, thus controlling, for example, the growth of tumors[3]. This is why there is a higher incidence of tumors in the elderly [3].

Through the action of NK cells and $CD8^+$ T cells, the immune system is able to eliminate any cells whose surface protein expression indicates signs of damage and/or malignant transformation. During senescence, there is a significant reduction in the ability of immune cells to fight pathogens, leading to chronic infection [4]. A classic example of senescent cell control and elimination is the red blood cells. Mature red blood cells are anucleated cells whose half-life is approximately 115 days. After this period they become senescent, with the gradual deterioration of their capacity, and they are subsequently eliminated in the spleen. Red blood cells have surface molecules that signal their state of senescence, indicating the right time to eliminate them. The formation of band 3 protein aggregates (one of the most abundant red cell transmembrane proteins), when stabilized by oxidized hemoglobin molecules (hemichromes), are recognized as antigens by autologous IgG antibodies and complement system. With the deposition of a critical density of antibodies and complement molecules, senescent red blood cells are recognized and eliminated [5].

The senescent red blood cells expose phosphatidylserine on the outer portion of their plasma membrane, a sign that indicates that the cell should be phagocytosed. In healthy cells this phospholipid is actively maintained in the cytoplasmic portion of the plasma membrane. Concomitantly, there is down-regulation of the CD47 molecule, a transmembrane protein whose normal expression indicates a non-phagocytic signal. The exposure of phosphatidylserine coupled with the reduction of CD47 expression stimulates phagocytosis and the elimination of these red blood cells [6]. In 2001, Bratosin [7] and colleagues described a process similar to apoptosis occurring in red blood cells, later called erythrosis [8]. Eryptosis has several similarities to apoptosis, regardless of the trigger, induction of an eripotic state usually involves extracellular calcium entry into the cell, caspase and calpain activation, which causes changes in membrane asymmetry, phosphatidylserine exposure and cell shrinkage. and membrane. Erythrosis has been associated with several pathologies, including metabolic syndromes, uremic syndromes, anemias such as sickle cell anemia and thalassemia, and can be triggered by several signs, including osmotic shock and xenobiotics [5].

Infectious processes also induce erythrosis, such as *Plasmodium* infection that cause malaria [5]. Infection with *P. falciparum* induces oxidative stress, promoting the opening of calcium channels. Erythrosis also appears to be induced in uninfected red blood cells, both in *P. yoelii* [9] and *P. falciparum* infections [10]. That is, chronic infection during malaria induces early red blood cell senescence. Autophagy is a physiological mechanism that allows cells to recognize damaged proteins or organelles and destroy them. In situations of mitochondrial stress, such as the increase of reactive oxygen species, autophagic processes may induce apoptosis cell death [11]. Autophagy also participates in the protection against some intracellular pathogens, although some are able to escape phagolysosome degradation. The relationship between autophagy and senescence is that the latter is characterized precisely by cells resistant to apoptosis and whose autophagic processes do not occur [12].

Like malaria, other chronic infections can also induce host aging. Some bacteria, viruses and protozoa are capable of causing tissue stress leading to molecular and physiological changes in host cells leading to a senescence process. In individuals with cystic fibrosis caused by

Pseudomonas aeruginosa, it is believed that the pyocyanin bacterial toxin prevents autophagy. This is due to the increased production of reactive oxygen species, preventing the scaling of the pulmonary epithelium and thus facilitating bacterial colonization [13]. Furthermore, chronic infection with *Chlamydia trachomatis*, induces increased DNA methylation, and consequently senescence [14].

In infection with *Mycobacterium tuberculosis*, it is believed that autophagy would function as a protective factor against infection, representing an efficient antimicrobial factor. Although the bacterial toxin ESAT-6 inhibits autophagosome maturation, it is believed that inhibition of autophagy is an activated factor of senescence, so factors that induce autophagosome maturation, such as IFN-gamma, would be inhibitors of senescenia [3]. Coinfection between *M. tuberculosis* and HIV induces high viremia and functionally altered $CD8^+$ T lymphocytes, which are associated with increased expression of cellular markers associated with this characteristic, as well as the absence of other activation factors such as perforins, granzymes and intracellular IFN-gamma [15].

This state of T lymphocytes is compatible with immunosenescence, which is the aging of the immune system that can be caused by chronic infections, such as HIV, *Plasmodium* spp., or also by tumors [16]. As with *M. tuberculosis* infection, *Trypanosoma cruzi* infection is another example of a chronic infection that induces host senescence related to autophagy blockade [17]. In Chagas disease, we observed lymphopenia and signs of T-cell senescence. In patients infected with *T. cruzi*, $CD8^+$ and $CD4^+$ T cells display markers of immunosensitivity and show a depleted functional phenotype with decreased production of IFN-gamma and IL-23. Along with evasion of the immune system, *T. cruzi* can also prevent autophageal intracellular degradation by compromising autophagosome maturation. Autophagy blockade contributes, as the protection of cellular stress, to the activation of senescence [3].

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