

Researchers propose new vision of process wrongly associated with ageing

July 14 2014

For the Spanish Royal Academy, senescent is he who "begins to age". But laboratory biology results are contradicting the dictionary: not only is senescence not a synonym of ageing, it is also not intrinsically negative for the organism. Cellular senescence is such a badly named physiological process that those who do research in this area think it needs another name. That is the case of Manuel Serrano, from the Spanish National Cancer Research Centre (CNIO), one of the world's leading experts on senescence, who has just published a review on this topic. Without actually renaming senescence, this edition of *Nature Reviews* promotes a paradigm shift: senescence is, above all, "a mechanism to eliminate unwanted cells", which ends with the remodelling of tissues. And it can be something of a double-edged sword for the body.

More than five decades ago, Leonard Hayflick and Paul Moorhead discovered that healthy human cells growing in culture stop proliferating after a certain number of divisions. They called the phenomenon cellular senescence and postulated that it could be the cause of ageing in the body. But more recent research, led largely by Serrano and his group—Daniel Muñoz-Espín is co-author of the current revision—has shown that this pioneering observation only told part of the story.

Today, we know that the relationship between senescence and ageing resembles that between firemen and fire: although there are many firemen at a fire, they are not the cause of the blaze but rather an attempt to put it out. In a similar way, Serrano and Muñoz-Espín propose that

senescence activates when there is damage to a cell, to prevent it from spreading or even to repair the affected tissue. In ageing organisms, what happens is that the process stops halfway with a large number of [senescent cells](#) present in the tissues.

The authors talk of a sequence of events: "Senescence-clearance-regeneration". "Recent discoveries are redefining our vision of [cellular senescence](#)", they write. To achieve their goal: "senescent cells inhibit their own proliferation, induce their own elimination by attracting cells from the immune system and finally promote tissue regeneration". In aged tissues or with certain diseases, however: "this sequence is not completed, and the senescent cells accumulate".

That is why: "senescence can become part of the problem with ageing, instead of the solution", write the authors.

Today it is known that cells initiate their senescence programme in response to stimulants such as the activation of different oncogenes—cancer-causing genes; the absence or malfunction of anti-cancer genes; or the shortening of telomeres, the protein structures that protect the ends of chromosomes. All of these stimulants damage cells and senescence then works as a protective mechanism.

Furthermore, Serrano and Muñoz-Espín have recently discovered that senescence intervenes in another key process for the organism, in a stage very far removed from ageing: development. As the embryo grows, it needs to get rid of or redesign physiological structures, and the genetic orders it uses to that end are those related to senescence.

This discovery has allowed these researchers to complete their vision of senescence as a mechanism that is really there to: "eliminate unwanted cells" and end up regenerating tissue, even with a different than the one it had previously.

In this new vision, therefore, senescence is just a physiological mechanism. The question is: should we stimulate it, to fight cancer, for example, or should we prevent it, to stop ageing? Both, say the researchers.

The revision presents a list of pathologies in which senescence can have either a beneficial or harmful effect. In several types of cancer, for example, senescence stops the advance of the disease; in cardiovascular disease, it restricts atheroma formation; it is also beneficial against several types of fibrosis. With obesity and diabetes, however, it favours disease development, increasing resistance to insulin and inflammation.

Clinical research also reflects the two faces of senescence, given that both therapies based on promoting it—specifically against cancer and kidney and liver fibrosis—and on stopping it are being studied. The authors underline the success in breast cancer trials of a new drug that stimulates senescence: palbociclib.

But they leave one mystery unsolved: moles. Nowadays we know that moles are collections of senescent cells that have not been eliminated. Why? To be continued.

More information: Cellular senescence: from physiology to pathology. Muñoz-Espín D, Serrano M. *Nature Reviews Molecular Cell Biology* (2014). [DOI: 10.1038/nrm3823](https://doi.org/10.1038/nrm3823)

Provided by Centro Nacional de Investigaciones Oncológicas (CNIO)

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