MedicalXpress

Spanish researchers describe the nine hallmarks of aging

June 6 2013

For some species, living twice as long in good health depends on no more than a few genes. When this fact was revealed by studies on worms three decades ago, it ushered in a golden age of ageing studies that has delivered numerous results, but also sown some confusion. The journal *Cell* is now publishing an exhaustive review of the subject that aims to set things straight and "serve as a framework for future studies." All the molecular indicators of ageing in mammals – the nine signatures that mark the advance of time – are set out in its pages. And the authors also indicate which can be acted upon in order to prolong life, while debunking a few myths like the belief that antioxidants can delay aging.

The authors are Spanish scientists Maria Blasco (Spanish National Cancer Research Centre, CNIO), Carlos López-Otín (University of Oviedo), and Manuel Serrano (CNIO), along with Linda Partridge (Max Planck Institute for Biology of Ageing) and Guido Kroemer (Paris Descartes University). Their inspiration came from a classic 2000 paper, The Hallmarks of Cancer, also published in *Cell*, which marked a watershed in cancer research. Blasco, Serrano and Partridge contacted *Cell* proposing a similar effort to systematically review and organize the state of knowledge on aging; López-Otín and Kroemer had also come to the conclusion that this kind of analysis was much needed, and decided to share their ideas and efforts to get the project off the ground.

"The current situation of aging research exhibits many parallels with that of cancer research in previous decades," reads the opening paragraph of the resulting paper, titled The Hallmarks of Aging. "The aging field has

been notoriously more abundant in theories than experimental evidence," says Blasco; "this review doesn't discuss theories, but molecular and genetic evidence." For López-Otín "the time had come to set out in organized, understandable fashion the molecular keys to what is still a little known process, despite the thousands of scientific papers published on the subject every year."

The paper's connection with cancer goes beyond formal parallelisms. Because one of the main conclusions of The Hallmarks of Aging is that by understanding and combating aging we can also fight against cancer and the other diseases of most incidence in the developed world. The relationship is clear: aging is the result of the lifelong accumulation of DNA damage, and it is this same process that causes cancer, diabetes, cardiovascular disease and neurodegenerative conditions like Alzheimer's.

"Aging is the cause of the diseases that afflict us as we get older," Blasco explains. "Identifying the molecular markers of aging will help us find the cause of other diseases like cancer. The implications are enormous." As the article puts it, "cancer and aging share common origins," and can be regarded as "two different manifestations of the same underlying process."

"It's not about not having wrinkles"

For Serrano, this removes the "frivolity" with which aging research is often approached: "It's not about not having wrinkles or living to be a hundred at any cost, but about prolonging disease-free life." In *Cell* the scientists are explicit about their final goal, which is "to identify pharmaceutical targets to improve human health during aging."

Another milestone of the paper is that it not only defines the nine molecular hallmarks of aging but orders them into primary hallmarks –

the triggers; those that make up the organism's response to these triggers; and the functional defects resulting. This hierarchy is important, because different effects can be achieved by acting on one or other of these processes. By acting on just one mechanism, if it numbers among the primaries, we can delay the aging of many organs and tissues.

There are four primary causes of aging: genomic instability; the shortening of telomeres; epigenetic alterations; and loss of proteostasis.

Genomic instability refers to the defects the genes accumulate over time, due to intrinsic or extrinsic causes. The shortening of telomeres – the protective caps over the ends of chromosomes – is one such defect, but so important a one that it stands as a hallmark in its own right. Epigenetic alterations are the result of lived experience – our exposure to the environment.

Loss of proteostasis has to do with the non-elimination of defective proteins, whose accumulation promotes age-related diseases. With Alzheimer's, for instance, neurons die because plaques form of a protein that should have been eliminated.

The organism responds to these triggers with mechanisms that try to correct the damage, but which can themselves turn deleterious if they become exacerbated or chronic. This is the case of cellular senescence: the cell is induced to stop dividing, and thus prevent cancer, when too many defects are built up, but if the effect is overdone, the tissues – and the body – age.

This double-edged sword is also present in two processes at the heart of the debate on aging theories: the so-called oxidative damage, linked to the famous free radicals; and metabolism-derived mechanisms, relating, in turn, to the evidence – though not yet in humans – that calorie restriction prolongs life.

Free radicals: A double-edged sword

Everything suggests that the secret to living longer is a lot more complex than simply taking antioxidants or cutting out food. Free radicals may be harmful in large quantities, but their presence also triggers a protective response. As for antioxidants, the authors are adamant: there is no genetic evidence that enhancing antioxidant defenses can delay aging. And while the organism may deploy protective strategies to cope with nutrient scarcity – presumably the reason why calorie restriction appears to work –, these too "in excess and during time, can become pathological," they affirm.

The third group of hallmarks comes into play when the body cannot compensate the damage caused by the two preceding groups. One is the exhaustion of tissue stem cells, which cease to discharge their regenerating function; another is errors in intercellular communication, which give rise, for instance, to inflammation – a process whose chronic form is associated with cancer.

Among the next big challenges is to understand the connections between hallmarks. And, of course, to investigate ways to bring these processes under control. The authors run through the list of already identified therapeutic targets and propose some solutions to slow down aging.

One therapeutic strategy tested successfully in mice is to stop the telomeres from shortening. "The process can be halted and even reversed in mice," remarks Blasco, an expert in the area, who is convinced that, by and large, "we still have ample room for manoeuver to combat aging and enjoy more years of both life and health."

For López-Otín, "We have diverse opportunities to extend longevity in the not too distant future. Treatments aimed at reducing or correcting the genomic damage that occurs with time are still a distant prospect, but

those focusing on metabolic regulation systems may be much more achievable. We don't aspire to immortality, just to the possibility of making life a little better for us all."

More information: The Hallmarks of Aging. Carlos López-Otín, Maria A. Blasco, Linda Partridge, Manuel Serrano, Guido Kroemer. Cell (2013). doi: 10.1016/j.cell.2013.05.039

Provided by Centro Nacional de Investigaciones Oncologicas (CNIO)

Citation: Spanish researchers describe the nine hallmarks of aging (2013, June 6) retrieved 8 May 2024 from https://medicalxpress.com/news/2013-06-spanish-hallmarks-aging.html

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