

Press release
September 22, 2023

Countering the effects of aging and the occurrence of cancers: new and promising results

Cancer and aging are closely linked processes, but the mechanisms underlying this relationship are still not well understood. By studying immune cells in the lung, researchers from Institut Curie and Inserm have provided new knowledge on the topic. They show that targeting ruptures of the nuclear envelope of these cells would represent a new opportunity for therapeutic intervention in age-related diseases, in particular cancer, thus improving the quality of life of the elderly in the long term. Funded by the Fondation ARC, this work has just been published in the journal *Nature Aging*.

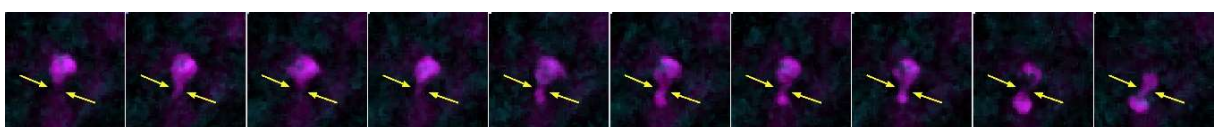
Age is one of the main risk factors for the development of a number of diseases, such as viral or bacterial infections and neuro-degenerative diseases, but also cancers. The economic and societal issues related to the overall aging of the population constitute a major challenge. Furthermore, the notion of "healthy aging" increasingly suggests that targeting aging rather than its consequences is a far better strategy for reducing morbidity among the elderly.

More than two thirds of new cancers diagnosed in France occur in people over the age of 65¹. The appearance of cancers with age can be explained by the accumulation of genetic alterations during a lifetime, less effective DNA repair mechanisms, and also by an **aging immune system with diminished protective functions (immunosenescence)**. What are the mechanisms that govern this phenomenon? How can we develop strategies to counter immunosenescence?

The nucleus of immune cells sensitive to deformations

It is these questions that the Inserm and Institut Curie researchers attempted to answer. With time, DNA becomes fragile and one of the characteristic markers of cell aging is genome instability. When they patrol through the various tissues within the body, the immune system cells are sensitive to deformations which weaken their nucleus and promote DNA breakage. **To maintain the structure of the nucleus and thus the genome's integrity, the cell relies on a dense network of proteins, which include lamins.** Among them lamin A/C is studied in particular since it undergoes alterations over the course of aging. In addition, mutations in the gene coding for this protein are known to cause early aging syndromes.

"Repeated ruptures of the nuclear envelope lead to DNA damage. It is vital to understand the processes at work in this regard since they promote not just aging of the body, but also the development of cancers. For example, ruptures of the nucleus make the DNA "visible" by damaging proteins, thus triggering a response from the cell that will promote the development of metastases", explains **Dr. Nicolas Manel**, Inserm research director and team leader at Institut Curie.



"Two-photon" microscopy of the extreme deformation of an alveolar macrophage, when it passes between two alveoli. During these migrations the nucleus is also deformed, and it is at this point that the DNA can be damaged.

¹ Source INCa: <https://www.e-cancer.fr/Professionnels-de-sante/L-organisation-de-l-offre-de-soins/Oncogeriatric/Epidemiologie>

A protein identified in the lung: lamin A/C

At Institut Curie, the Innate Immunity team of Dr. Nicolas Manel, Inserm research director, studied a new experimental model in which the immune system's cells are deficient in lamin A/C. Researchers looked closely at a population of lung macrophages - alveolar macrophages - which are highly dependent on lamin A/C for their survival. The role of these alveolar macrophages is to constantly monitor the lungs, and they are one of the main entry points for a number of pathogens.

The researchers showed that without lamin A/C, the alveolar macrophages show serious signs of fractures in their nucleus and damage to the DNA, leading to a dramatic drop in their number in the lungs. Furthermore, the surviving alveolar macrophages have many characteristics similar to those of aged alveolar macrophages, and accumulate markers characteristic of aging. The team also revealed that **without lamin A/C in the macrophages, the implantation and growth of lung tumors is a lot faster, encouraged by the malfunction of the aged macrophages.**

The loss of lamin A/C would therefore constitute a mechanism for alveolar macrophage aging and a prime study model for understanding how lung cancers develop in the elderly. "Our results open up many new opportunities for studying aging of the immune system, caused by rupture of the nuclear envelope and the decrease in its effectiveness against infections and tumors, in the lungs but also in other organs", concludes Dr. Nicolas Manel.

These studies are funded in the amount of 2.5 million euros as part of the call for projects "Cancer and Aging" of Fondation ARC for cancer research.

Reference: De Silva, N.S., Siewiera, J., Alkhoury, C. et al. [Nuclear envelope disruption triggers hallmarks of aging in lung alveolar macrophages](https://doi.org/10.1038/s43587-023-00488-w). Nature Aging (2023). <https://doi.org/10.1038/s43587-023-00488-w>

Press contacts

Elsa Champion – elsa.champion@curie.fr/+33(0)7 64 43 09 28/

Catherine Goupillon-Senghor - catherine.goupillon-senghor@curie.fr/+33(0) 6 13 91 63 63

Juliette Mamelonet - juliette.mamelonet@havas.com/+33(0)1 58 47 90 12

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About Inserm

Founded in 1964, Inserm is a public scientific and technological institute which operates under the joint authority of the French Ministries of Health and Research. The institute is dedicated to biomedical research and human health, and is involved in the entire range of activities from the laboratory to the patient's bedside. It also partners with the most prestigious research institutions in the world that are committed to scientific challenges and progress in these fields. <https://www.inserm.fr/>

About the Fondation ARC for cancer research

The Fondation ARC is based on the conviction that research will beat cancer. It is thanks to the discoveries of these researchers that we will achieve victory.

Its mission is to unleash the extraordinary potential of French research in oncology by providing strategic material and human resources. <https://www.fondation-arc.org/>