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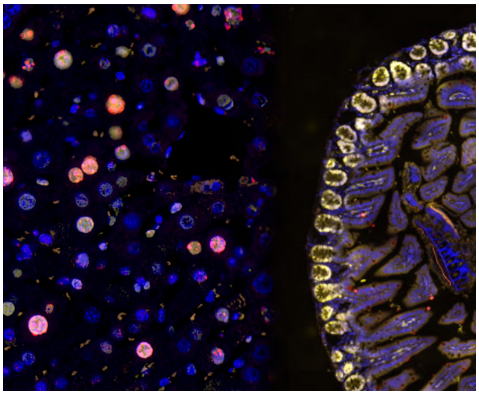
Why some organs age faster than others

Scientists at the UNIGE, Bern Inselpital and UNIBE have discovered that hidden mutations in non-coding DNA are responsible for the ageing of certain tissues, such as those in the liver.

The accumulation of mutations in DNA is often mentioned as an explanation for the ageing process, but it remains just one hypothesis among many. A team from the University of Geneva (UNIGE), in collaboration with the Inselspital, University Hospital of Bern and the University of Bern (UNIBE), has identified a mechanism that explains why certain organs, such as the liver, age more rapidly than others. It reveals that damages to non-coding DNA, which are often hidden, accumulate more in slowly proliferating tissues, such as those of the liver or kidneys. Unlike in organs that regenerate frequently, these damages remain undetected for a long time and prevent cell division. These results, published in the journal *Cell*, open new avenues for understanding cellular ageing and potentially slowing it down.

Our organs and tissues do not all age at the same rate. Ageing, marked by an increase in senescent cells - cells that are unable to divide and have lost their functions - affects the liver or kidneys more rapidly than the skin or intestine. The mechanisms that contribute to this process are the subject of much debate within the scientific community. While it is widely accepted that damage to the genetic material (DNA), which accumulates with age, is at the root of ageing, the link between the two phenomena remains unclear.

DNA molecules contain coding regions - the genes that code for proteins - and non-coding regions that are involved in the mechanisms that regulate or organize the genome. Constantly damaged by external and internal factors, the cell has DNA repair systems that prevent the accumulation of errors. Errors located in the coding regions are detected when genes are transcribed, i.e. when they are activated. Errors in non-coding regions are detected during cell renewal, which requires the creation of a new copy of the genome each time, via the process of DNA replication. However, cell renewal does not occur with the same frequency depending on the type of tissue or organ.



Liver cells with DNA damage are stained red (left). Proliferating intestine cells, with no DNA damage, are stained yellow (right).

High resolution pictures

Tissues and organs that are in constant contact with the outside environment, such as the skin or intestine, renew their cells (and therefore replicate their DNA) more often - once or twice a week - than internal organs, such as the liver or kidneys, whose cells proliferate only a few times per year.

The liver as the ideal model for studying ageing

The group led by Thanos Halazonetis, full professor in the Department of Molecular and Cellular Biology at the UNIGE Faculty of Science, is studying the mechanisms of DNA replication. His team, in

collaboration with the groups led by Prof. Stroka and Prof. Candinas at the Inselspital in Bern and UNIBE, has been studying liver cells (hepatocytes), which proliferate infrequently. The scientists analyzed the potential link between the more rapid ageing of the liver and the lower frequency of DNA replication in its cells.

"Our study model, the mouse liver, is an ideal organ for studying the mechanisms of DNA replication in vivo. In adult mammals, hepatocytes rarely proliferate unless they have been partially ablated. After ablating two-thirds of the livers of young or old mice, we can study the replication mechanisms in a young or ageing organ, directly in the living organism", explains Prof. Deborah Stroka, co-last author of the study.

By mapping for the first time the sites at which DNA replication starts in liver cells that regenerate after ablation, the scientists discovered that these are always located in non-coding regions. It was also observed that replication initiation was much more efficient in young mice than in old mice.

"These non-coding regions are not subject to regular error checking and therefore accumulate damage over time. After removal of the liver in young mice, there is still little damage and DNA replication is possible. On the contrary, when the experiment is carried out in old mice, the excessive number of errors accumulated over time triggers an alarm system that prevents DNA replication," explains Giacomo Rossetti, research fellow in the Department of Molecular and Cellular Biology at the UNIGE Faculty of Science and first author of the study. This block of DNA replication prevents cells from proliferating, leading to degradation of cell functions and tissue senescence.

Hope for slowing down the ageing process

These observations could help explain why slowly proliferating tissues, such as the liver, age faster than rapidly proliferating tissues, such as the intestine. In cells that have remained dormant for long periods, too many cryptic DNA lesions have accumulated in the non-coding regions, which contain the origins of replication, and prevent replication from being triggered. In rapidly proliferating tissues, on the other hand, little damage accumulates thanks to frequent cell renewal, and the origins of replication retain their efficiency.

"Our model suggests that by repairing cryptic DNA damage before replication is triggered, certain aspects of ageing could perhaps be avoided. It is on this new working hypothesis that our efforts will focus", concludes Thanos Halazonetis.

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