

Study Identifies New Cause of Age-Related Inflammation, Suggesting Promising Treatment Pathway

In preclinical models, Xpovio suppressed inflammaging, reduced liver fibrosis, lowered inflammatory markers and extended lifespan.

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- As cells age, they increasingly export nucleic acid structures called R-loops from the nucleus, triggering an immune response that causes harmful inflammation.
- This study identified a two-protein complex involved in exporting R-loops and tested an approved drug to block this process.
- Results in preclinical models showed decreases in age-associated inflammation, liver damage, fat gain and muscle loss, as well as a significant increase in lifespan.
- The drug, called KPT-330 (selinexor [Xpovio]), already is FDA-approved to treat multiple myeloma.

A new study led by researchers at The University of Texas MD Anderson Cancer Center has uncovered a previously unknown connection between nucleic acid structures called R-loops and age-related inflammation – or inflammaging – that could herald new intervention options for chronic inflammation and the subsequent health conditions.

The study, published in [Nature Aging](#), was led by [Rugang Zhang, Ph.D.](#), professor and chair of [Experimental Therapeutics](#). The researchers identified two specific proteins involved in the export of R-loops, a process that leads to inflammaging and related health issues. In preclinical models, the administration of KPT-330 prevented the R-loops from being exported and led to significant improvement in inflammation, liver damage, fat gain, muscle loss and overall lifespan.

“Chronic, widespread inflammation is a driving factor in many age-related diseases, including cancer, and our research has discovered one reason why this happens,” Zhang said.

“Understanding the cause is the first step toward developing treatments. We saw encouraging results using a drug that has already been tested in humans, paving the way for potential clinical use to alleviate age-related conditions.”

What are R-loops and how do they impact inflammation?

As cells age, they stop dividing and enter a “retired” state called senescence, when they begin releasing inflammatory signals that contribute to chronic inflammation. Previously, limited knowledge existed about why these inflammatory signals are released, but researchers have now pinpointed R-loops as a key component.

An R-loop is a temporary cellular structure created during the transcription process, when a double strand of RNA and DNA becomes tangled with a third displaced single strand of DNA. Normally, R-loops are confined to the cell nucleus. This study found that cells in senescence increasingly export R-loops into the cytoplasm, or the fluid between the cell membrane and the nucleus.

The exported R-loops attach to fragments of DNA debris in the cytoplasm, alerting the immune system, which mistakes the R-loops for a threat and triggers inflammation. This process creates widespread, chronic inflammation, similar to an alarm that won’t turn off.

This study identified the two proteins involved in exporting R-loops, DDX1 and XPO1. DDX1 attaches to the R-loop inside the nucleus and carries it outside. XPO1 acts as an “exit gate” from the nucleus, allowing the R-loops to be transported into the cytoplasm by forming a complex with DDX1.

How does a drug approved for cancer treatment help alleviate inflammation?

R-loop export and DNA debris forming in the cytoplasm happen independently. An immune response is only activated when the two connect, meaning it may be possible to block one without affecting the other.

Researchers tested this theory by administering KPT-330, a Food and Drug Administration-approved drug for treating multiple myeloma by blocking nuclear export. With no exit, the R-loops remain trapped inside the nucleus and can’t trigger an inflammatory response.

In this study, shutting down nuclear export by blocking XPO1 in preclinical models suppressed inflammaging, reduced liver fibrosis, lowered systemic inflammatory markers, reversed age-related body composition changes, and significantly extended lifespan.

What’s next for this research?

Since KPT-330 already has been tested and proven safe for humans, these findings show translational promise for treating age-related conditions.

In a separate experiment, researchers found that the same inflammatory alarm helps the immune system find and eliminate precancerous cells, indicating a need to refine the alarm rather than silence it altogether. With DDX1 identified as the delivery mechanism transporting R-loops outside the nucleus, future studies could explore blocking that protein instead of shutting down all nuclear export, potentially causing fewer side effects.

Further investigation is still needed regarding why cells export more R-loops as they age. Understanding these mechanisms could lead to more refined strategies for overcoming the effects associated with senescent cells.

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