Rejuvenating old organs could increase donor pool

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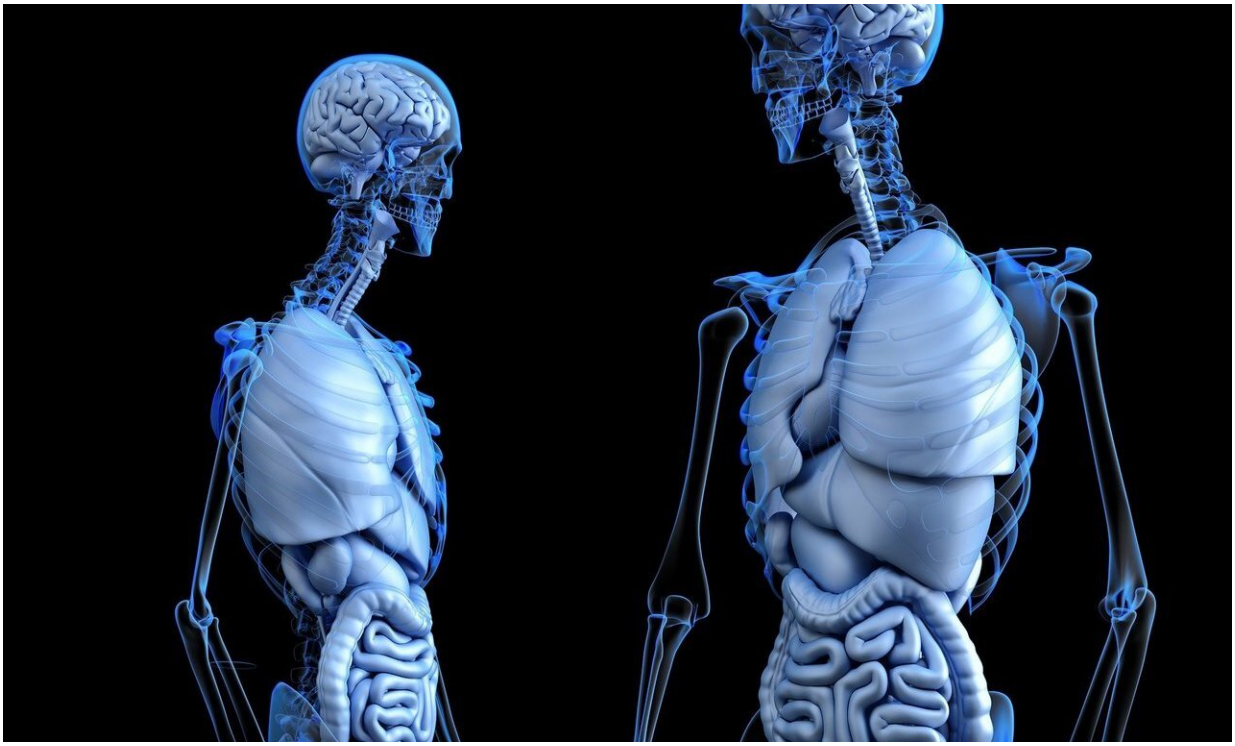

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Despite the limited supply of organs available for patients on waitlists for transplantation, organs from older, deceased donors are frequently discarded or not utilized. Available older organs have the potential to close the gap between demand and supply that is responsible for the very long wait-times that lead to many patients not surviving the time it takes

for an organ to become available. Older organs can also often provoke a stronger immune response and may put patients at greater risk of adverse outcomes and transplant rejection. But, as the world population ages, organs from older, deceased donors represent an untapped and growing resource for patients in need. Investigators from Brigham and Women's Hospital are leading efforts to breathe new life into older organs by leveraging a new class of drugs known as senolytics, which target and eliminate old cells. Using clinical and experimental studies, the team presents evidence that senolytic drugs may help rejuvenate older organs, which could lead to better outcomes and a wider pool of organs eligible for donation. Results are published in *Nature Communications*.

"Older organs are available and have the potential to contribute to mitigating the current demand for organ transplantation," said corresponding author Stefan G. Tullius, MD, Ph.D., chief of the Division of Transplant Surgery at the Brigham. "If we can utilize older organs in a safe way with outcomes that are comparable, we will take a substantial step forward for helping patients."

As organs age, senescent cells accumulate. These cells, which no longer divide, escape the body's usual means of destroying older, unneeded cells. Senescent cells release cell-free mitochondrial DNA (mt-DNA), which also accumulates in older organs. Recent studies have suggested that this rise in mt-DNA is tied to organ rejection.

In their Nature Communications paper, Tullius and colleagues identified senescent cells as the key source of mt-DNA and present evidence that the accumulation of mt-DNA provokes an immune response leading to organ failure and rejection. Senolytic drugs force senescent cells back into the cell cycle, allowing the body to clear them. The researchers therefore examined whether senolytic drugs could be used to improve outcomes. In a mouse model, they treated organ donors with a combination of the senolytic drugs dasatinib and quercetin. The drugs

reduced the number of senescent cells, reduced mt-DNA levels and decreased inflammation. Most relevantly, the survival of old organs treated with senolytics was as comparable to that of organs originating from young donors.

Since the authors carried out their therapeutic experiments in a mouse model, further mechanistic studies are needed to evaluate whether senolytic drugs may have the same effects on human organs from older donors and the same degree of success in clearing senescent cells, as well as whether organs can be treated effectively with senolytic drugs after they are harvested. The authors have already started with first steps in humans and determined that augmented levels of mt-DNA circulate in older organ donors.

"We have not yet tested the effects clinically, but we are well prepared to take the next step toward clinical application by using a perfusion device to flow senolytic drugs over organs and measure whether or not there are improvements in levels of senescent cells," said Tullius. "Our data provide a rationale for considering clinical trials treating donors, organs, and/or recipients with senolytic drugs to optimize the use of organs from older donors. The goal is to help to close the gap between organ availability and the needs of the many patients currently on transplant waiting lists."

More information: Jasper Iske et al, Senolytics prevent mt-DNA-induced inflammation and promote the survival of aged organs following transplantation, *Nature Communications* (2020). DOI: 10.1038/s41467-020-18039-x

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