

Senolytic drugs reverse damage caused by senescent cells in mice

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Injecting senescent cells into young mice results in a loss of health and function but treating the mice with a combination of two existing drugs cleared the senescent cells from tissues and restored physical function. The drugs also extended both life span and health span in naturally aging mice, according to a new study in *Nature Medicine*, published on July 9, 2018. The research was supported primarily by the National Institute on Aging (NIA), part of the National Institutes of Health (NIH).

A research team led by James L. Kirkland, M.D., Ph.D., of the Mayo Clinic in Rochester, Minnesota, found that injecting even a small number of senescent cells into young, healthy mice causes damage that can result in physical dysfunction. The researchers also found that treatment with a combination of dasatinib and quercetin could prevent cell damage, delay physical dysfunction, and, when used in naturally aging mice, extend their life span.

"This study provides compelling evidence that targeting a fundamental aging process—in this case, cell senescence in mice—can delay age-related conditions, resulting in better health and longer life," said NIA Director Richard J. Hodes, M.D. "This study also shows the value of investigating biological mechanisms which may lead to better understanding of the aging process."

Many normal cells continuously grow, die, and replicate. Cell senescence is a process in which cells lose function, including the ability to divide and replicate, but are resistant to cell death. Such cells have been shown

to affect neighboring ones because they secrete several pro-inflammatory and tissue remodeling molecules. Senescent cells increase in many tissues with aging; they also occur in organs associated with many chronic diseases and after radiation or chemotherapy.

Senolytics are a class of drugs that selectively eliminate senescent cells. In this study, Kirkland's team used a combination of dasatinib and quercetin (D+Q) to test whether this senolytic combination could slow physical dysfunction caused by senescent cells. Dasatinib is used to treat some forms of leukemia; quercetin is a plant flavanol found in some fruits and vegetables.

To determine whether senescent cells caused physical dysfunction, the researchers first injected young (four-month-old) mice with either senescent (SEN) cells or non-senescent control (CON) cells. As early as two weeks after transplantation, the SEN mice showed impaired physical function as determined by maximum walking speed, muscle strength, physical endurance, daily activity, food intake, and body weight. In addition, the researchers saw increased numbers of senescent cells, beyond what was injected, suggesting a propagation of the senescence effect into neighboring cells.

To then analyze whether a senolytic compound could stop or delay physical dysfunction, researchers treated both SEN and CON mice for three days with the D+Q compound mix. They found that D+Q selectively killed [senescent cells](#) and slowed the deterioration in walking speed, endurance, and grip strength in the SEN mice.

In addition to young mice injected with [senescent cells](#), the researchers also tested older (20-month-old), non-transplanted mice with D+Q intermittently for 4 months. D+Q alleviated normal age-related physical dysfunction, resulting in higher walking speed, treadmill endurance, grip strength, and daily activity.

Finally, the researchers found that treating very old (24- to 27-month-old) mice with D+Q biweekly led to a 36 percent higher average post-treatment life span and lower mortality hazard than control mice. This indicates that senolytics can reduce risk of death in old mice.

"This is exciting research," said Felipe Sierra, Ph.D., director of NIA's Division of Aging Biology. "This study clearly demonstrates that senolytics can relieve physical dysfunction in [mice](#). Additional research will be necessary to determine if compounds, like the one used in this study, are safe and effective in clinical trials with people."

The researchers noted that current and future preclinical studies may show that senolytics could be used to enhance life span not only in older people, but also in cancer survivors treated with senescence-inducing radiation or chemotherapy and people with a range of senescence-associated chronic diseases.

More information: Senolytics improve physical function and increase lifespan in old age, *Nature Medicine* (2018). [DOI: 10.1038/s41591-018-0092-9](https://doi.org/10.1038/s41591-018-0092-9) , www.nature.com/articles/s41591-018-0092-9

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