Researchers discover first broad spectrum drug that can potently kill aging cells in culture

Published on December 15, 2015 at 6:32 AM

Researchers from the University of Arkansas for Medical Sciences (UAMS) and other institutions are reporting the discovery of the first broad spectrum drug that can potently kill senescent (or aging) cells in culture and effectively clear the cells in animals by specifically targeting a pathway that is critical for the survival of senescent cells.

Findings from the researchers were published today in a report in the online edition of *Nature Medicine* in advance of the scientific journal's print edition.

Because senescent cells are believed to play a role in the late effects of radiation on normal tissues and certain age-related diseases, this study has broad implications for future therapies targeting the common biological mechanism that contributes to late tissue injury caused by radiation and aging.

Cellular senescence, the loss of cells' ability to divide, normally functions as a tumor suppressive mechanism; however, senescent cells become "toxic" as they accumulate after exposure to radiation and with age. This is because they cause stem cell aging that reduces the ability of tissue regeneration and repair and drive chronic inflammation and oxidative stress.

Since chronic inflammation and oxidative stress are thought to be the root cause of some late effects of radiation and many age-related diseases, including radiation-induced long-term bone marrow injury and age-related osteoarthritis and atherosclerosis, eliminating senescent cells has the potential to mitigate radiation-induced late tissue injury and treat many age-related diseases.

A Nature 2011 publication showed that genetic clearance of senescent cells from a progeroid animal is beneficial, leading to delayed onset of age-related phenotypes.

In the current study, ABT-263, a molecule initially developed as an anti-cancer therapy, was given orally to either normally aged mice or irradiated mice to induce premature aging of the hematopoietic system, the organs and tissues involved in production of blood. ABT-263 effectively depleted senescent cells, including senescent "stem cells" of the bone marrow and muscle. Depletion of the senescent cells appeared to reduce premature aging of the bone marrow caused by irradiation, and even rejuvenated the function of stem cells in normally aged mice.

"Our results demonstrate that clearance of senescent cells by a pharmacological agent is beneficial in part by rejuvenating aged tissue stem cells. Because a decline in tissue stem cell function is associated with exposure to radiation and aging, we believe clearing senescent cells and rejuvenation of tissue stem cells could have a major impact on mitigation of radiation injury and treatment of diseases of aging," said Daohong Zhou, M.D., the senior author of the Nature Medicine publication, a professor of Pharmaceutical Sciences and the deputy director of the Division of Radiation Health in the UAMS College of Pharmacy.

"ABT-263 was originally developed as an anti-cancer agent. It has toxic side effects that make it inappropriate for development as an agent for diseases of aging. We are investigating next-generation small-molecule drugs that are optimized to clear senescent cells without drug-induced toxicity," Zhou said.

Source:
University of Arkansas for Medical Sciences
