



The Medical **Bulletin**

In Geriatrics

SOMETHING NEW ON AGING

Non-pituitary growth hormone (npGH) activation in the colon seems to play a key role in the aging process, setting the stage for age-associated diseases such as cancer.

"This is a pre-clinical study...targeting cancer and cardiovascular disease, as they are primarily associated with micro-environmental tissue changes," Dr. Shlomo Melmed of Cedars Sinai in Los Angeles told Reuters Health by email and in CELL reports. "We are elucidating mechanisms underlying the impact of GH on senescence at the cell level, including looking at cell-specific mRNA changes in response to GH in the aging cell."

One of the hallmarks of aging is accumulated damage to DNA and deficiencies in DNA repair that cause mutations and age-associated chromosomal abnormalities. Persistent DNA damage may also block cell proliferation, resulting in senescence and cell death, thereby further driving the aging process.

Specifically, DNA damage triggers the phosphorylation of the ataxia-telangiectasia-mutated (ATM) gene, which is responsible for repairing DNA damage and stabilizing the tumor suppressor, p53. However, ATM expression and activity deteriorate with age, likely resulting in age-related p53 loss and accumulated DNA damage.

To delve more deeply into the DNA repair process in the colon, the researchers used human intestinal organoids - three-dimensional stem cell-derived cultures that resemble human colon tissue. They found that organoids cultured up to four months exhibited aging markers, decreased telomere length and DNA damage accumulation, with increased npGH, suppressed p53, and attenuated DNA damage repair.

Suppressing GH in the older organoids increased p53 and decreased DNA damage. Similarly, wild-type mice showed age-dependent colon DNA damage accumulation, whereas in an older mouse model lacking colon GH signaling, DNA damage remained low, and p53 was elevated.

The authors conclude, "As age-associated npGH induction enables a pro-proliferative microenvironment, abrogating npGH signaling could be targeted as anti-aging therapy by impeding DNA damage and age-related pathologies."

Dr. Melmed said, "We will be doing drug screening to determine which senolytic is most effective in blocking GH signaling; Pegvisomant, an approved GH receptor blocker (used to treat acromegaly) is also being tested."

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