Reducing p38MAPK levels delays aging of multiple tissues in lab mice

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In the new issue of the *Developmental Cell* journal, a team of scientists at Singapore's Agency for Science, Technology and Research (A*STAR) and the University of North Carolina School of Medicine at Chapel Hill, report research findings about the molecular mechanisms behind the aging process, which has up till now been poorly understood, that offer the possibility that a novel, pharmacological approach could be developed to combat age-related disorders.

In their research with lab rodents, the scientists found that the p38MAPK protein, already known for its role in inflammation, also promotes aging when it activates another protein p16, which has long been linked to aging.

In addition, they found that reducing the levels of p38MAPK delayed the aging of multiple tissues.

Through their experiments, the scientists found that partial inactivation of p38MAPK was sufficient to prevent age-induced cellular changes in multiple tissues, as well as improve the proliferation and regeneration of islet cells, without affecting the tumour suppressor function of p16 in mice.

Dmitry Bulavin, M.D., Ph.D., research team leader and principal investigator in A*STAR's Institute of Molecular and Cell Biology (IMCB), said, "We are excited by this new found role for p38MAPK in aging. Due to the previously established involvement of p38MAPK in

inflammatory diseases, small molecule inhibitors of p38MAPK signalling have already entered clinical trials for the treatment of other medical conditions such as rheumatoid arthritis. Our latest discovery offers the possibility that a novel, pharmacological approach could be developed to combat age-related disorders."

In the paper, the scientists described how they studied the role of p38MAPK in aging by using genetically modified mice. They found that several organs, including the pancreas, in the mice that had a reduced amount of p38MAPK protein exhibited a delayed degeneration as the mice grew older.

These mice also displayed an improved growth and regeneration of pancreatic islet beta cells compared to the control group of mice with normal levels of p38MAPK. Beta cells make and release insulin.

In Type 2 diabetes, these cells are unable to produce enough insulin to meet the body's demand, partly due to a decrease in beta cell mass.

In addition, the scientists also found that the forced activation of p38MAPK stunted the growth of insulin-producing islet beta cells and caused insulin resistance in mice, which is the basis of Type 2 diabetes.

These results suggest that by controlling p38MAPK levels, scientists could potentially treat age-related degenerative conditions dependent on the p38MAPK signalling pathways.

Such findings may prove important to the development of novel treatment approaches for Type 2 diabetes in the elderly.

While investigating the effects of lowering p38MAPK levels to achieve a significant delay in aging in mice, the scientists had another consideration: insuring that the level of p16, a tumour suppressor, did

not fall below the threshold that was required to protect the animals from developing tumours.

Through their experiments, the scientists found that partial inactivation of p38MAPK was sufficient to prevent age-induced cellular changes in multiple tissues, as well as improve the proliferation and regeneration of islet cells, without affecting the tumour suppressor function of p16 in mice.

The scientists went on to investigate the upstream mechanisms that regulated p38MAPK in old mice and that have not been widely studied to date.

They found that high levels of the protein Wip1, a protein that has been known to be implicated in cancer, suppressed the activity of p38MAPK, and this led to islet proliferation, which in turn improved the pancreatic function in aging mice.

Their results, therefore, identified Wip1 as an additional target to which anti-aging therapies could be directed.

Neal Copeland, Ph.D., Executive Director of IMCB, said, "Dr. Bulavin's team has achieved an important breakthrough in the study of ageing. These significant findings, together with other recent discoveries made by IMCB's scientists, illustrate how IMCB has worked with its international collaborators to fully harness the knowledge and tools of modern medical science, to increase understanding of the causes behind common human diseases. The resulting knowledge will hopefully contribute to the development of effective treatment for clinical conditions."

Source: Agency for Science, Technology and Research (A*STAR), Singapore