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METFORMIN AS A DRUG FOR SENOTHERAPY

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This report focuses on the drug Metformin and its application in senotherapy. Metformin, an oral hypoglycemic drug of the biguanide class primarily used to manage blood glucose levels in patients with type 2 diabetes, is also being investigated for its potential to enhance life expectancy and improve quality of life in senotherapy.

Metformin is known to increase the secretion of circulating glucagon-like peptide-1 (GLP-1), which is released by intestinal L cells in response to neural and nutritional stimuli. This leads to glucose-dependent insulin secretion. GLP-1 also reduces appetite, contributing to weight loss. As a result, it can be utilized to treat obesity and delay the progression of diabetes.

Metformin stimulates adenosine monophosphate-activated protein kinase (AMPK), which acts as a fuel gauge, sensing when the cell is low on energy. It is a key sensor for maintaining the balance of the ATP-to-AMP ratio.

Metformin exhibits anticancer properties in both *in vitro* and *in vivo* conditions, mediated through AMPK activation. Liver kinase B1 (LKB1) is required to activate AMPK. Once activated, AMPK phosphorylates the transcriptional activator TorC2, blocking its nuclear translocation and inhibiting the gene for gluconeogenesis. The LKB1/AMPK signaling pathway plays a role in protecting against apoptosis, particularly in response to aging, which increases the AMP/ATP ratio. If this ratio cannot be reversed, the cell will undergo cell death.

Metformin, when used in conjunction with Doxorubicin, can be effective in treating cancer. While Doxorubicin alone shrinks tumors, they often regrow. However, when administered with metformin, tumors can be eradicated, and recurrence can be prevented. Metformin can also sensitize cancer cells to chemotherapy.

Metformin can be used in young patient who has asthma. A total of 464 patients with asthma from Arkansas (a state in America) school met with the criteria. Out patient worsening rate decreased after taking metformin prescription from 13.4% to 7.8%.

There's a recent study that says patients who take metformin as antidiabetic drug has low risk of getting dementia which is loss of cognitive functioning of the brain which are thinking, remembering and reasoning. Chronic obstructive pulmonary disease (COPD) is a disease which accelerates the aging of lungs with the accumulation of senescent cells. These senescent cells secrete multiple inflammatory proteins known as senescent-accociated secretory phenotype (SASP) which mimic the inflammatory mediators secreted in COPD. A major pathway leading to senescence is through that activation of phosphoinositide-3-kinase/ mammalian target of rapamycin (PI3K/mTOR) pathway. Anti-aging molecules such as sirtuin-1 and sirtuin-6 are reduced by phosphoinositide-3-kinase/ mammalian target of rapamycin pathway through microRNA-34a. Metformin inhibits the microRNA-34a and restores situation molecules which helps in anti-aging process in COPD. Telomere dysfunction is one of the main triggers to arteriosclerosis. Metformin induces telomere stabilization and inhibits vascular smooth muscle cell aging through arteriosclerosis. Metformin increases the phosphorylation of AMPK-dependent PGC-1alpha and increase telomere activity and increase the protein level of telomerase reverse transcriptase (TERT).

A study was done with ApoE KO mice, where it was fed with high fat diet and arteriosclerosis plaque was formed in the arteries of the mice. When metformin was given the size of the plaque did not reduce, but metformin inhibited the phosphorylation of AMPK/PGC1 alpha/TERT signaling cascade, which is associated with formation of plaque.

Metformin, a widely prescribed medication worldwide, is not only effective in reducing blood sugar levels but also exhibits numerous senotherapeutic effects, potentially enhancing both life expectancy and quality of life.