[Klotho Signaling Pathways] (KSP) Modulation by: Targets Active-Agents

Revised on 7/28/2023

Background / Grounded Truth Information:

The main objective of this prompt is to investigate the signaling / molecular pathways (A through O) utilized by the quarried Target-Agent(s). Target-Agents consist of any biologically active molecules that can modulate the identified molecular pathways involved in Klotho regulation. Target-Agents include drugs, small-molecules, nutraceuticals, nutritional supplements, minerals, metals, amino acids and vitamins. These pathways were screened prior to being quarried in this prompt because of their identified ability in peer reviewed literature to increase Klotho levels, by either downstream or upstream activation of the Klotho gene, or an increase in the secreted or soluble form of Klotho, commonly referred to as alpha-Klotho.

Klotho's background information and most recently described biological functions:
There are different forms of the Klotho (KL) protein, the transmembrane, soluble, and the secreted KL, which all perform distinct functions. Transmembrane KL makes a complex with fibroblast growth factor (FGF) receptors; for example, KL is also an obligate co-receptor for fibroblast growth factor 23 (FGF23). Transmembrane KL has a phosphaturic effect and also regulates the formation of active vitamin D, which is responsible for adequate calcium homeostasis]. In KL- or FGF23-deficient mice, not just phosphate retention but also premature aging syndrome has been shown, highlighting a possible association between phosphate metabolism and aging. Membrane-anchored proteases ADAM10 and ADAM17 can cleave and secrete the extracellular domain of KL into blood/serum, urine, and cerebrospinal fluid. Secreted KL regulates oxidative stress, growth factor receptors, and ion channels.

Soluble KL (sKL) functions as a circulating hormone and not only regulates multi- ple receptors and numerous ion channels, but is inversely associated with mortality. KL also inhibits the insulin/insulin-like growth factor 1 (IGF1) pathway, an evolutionarily conserved method for prolonging life. sKL protein is considered a powerful biomarker of longevity and contributes to anti-aging through calcium and phosphate metabolism regulation, inflammatory process

reduction, and oxidative stress protection. KL's tumor suppressive activity was first described in breast cancer, then in other solid tumors such as pancreatic cancer, cervical cancer, and melanoma. Although the exact molecular mechanism of KL in suppressing aging-related phenotypes is not well known, it appears that aging results in the methylation-dependent suppression of the KL gene expression, at least in monkeys. Indeed, methylation of DNA has been used to create epigenetic biomarkers of aging such as PhenoAge and GrimAge, which are sensitive markers of mortality and can also show the progress of aging. Acute and regular exercise can alter the level of circulating KL. However, the relationship between circulating KL and DNA methylation-based epigenetic clocks are unknown. We hypothesize that circulating KL is correlated with the age-associated methylation of the promoter region of the KL gene, and this is one of the reasons for the age-related decline in circulating KL. In addition, exercise status may affect circulatory KL levels.

(1Q) ("Molecular Pathway") (Column #1)

- Please list all (A through T), identified Molecular Pathways provided below by (Name) and (ID) Letters. Use only the ID letters and titles contained within (brackets), do not include any descriptive information. Please include all Pathways/categories listed below for each Target-Agent response. Please place this response in Column 1.

(2Q) ("Primary Biological Function")(Column2Q)

- One brief sentence detailing the primary Biological Function of this pathway. Please place this response in Column 2.

(3Q) ("Modulation Direction")(Column 3Q)

- Please indicate if the pathway is Activated, Down-Regulated, Modulated or Un-Affected by the target-agent. Place this response in column 3.

(4Q) ("Downstream Pathways or Cascades")(Column 4Q)

- One brief sentence detailing the downstream pathways or cascades, i.e., what is modulated next as a result of this pathway's modulation. Please place this response in Column 4.

(5Q) ("Synergistic Agents")(Column 5Q)

- All identifiable Target-Agents or small molecules or supplements that have demonstrated Additive, Complementary, or Synergistic activity with the quarried Target-Agent. IMPORTANT: Do not list signaling or molecular pathways in this column, only specific active agents ad defined by "Target-Agents," above. Please place this response in Column 5.

(6Q) ("Synergistic Agent Pathways")(Column 6Q)

- From the response provided in column 5, please provide the names of the molecular pathways that each synergistic agent modulates. Please place this response in Column 6.

Known Pathways:

First-Order, Molecular Pathways to be considered when returning each prompt query. Please note that this primary list should not exclude any others you determine to be relevant to upregulating any form of Klotho.

(A) {Klotho): transmembrane Klotho, soluble or α-Klotho
Klotho is a protein that has been shown to regulate aging and metabolism. SIRT1 upregulates Klotho gene expression in various tissues, including the brain, kidney, and liver. Klotho overexpression has been associated with increased lifespan and improved glucose homeostasis, and SIRT1 has been proposed to mediate these effects (13).

(B) (FGF23) or FGF23/Klotho Signaling Pathway

(C) (PI3K/Akt)

(D) (Insulin) / (IGF-1) Insulin and Insulin like Growth Factor) Signaling Pathway:

(E) (Epigenetic): changes in cell function that do not involve alterations to the DNA sequence, but access and control mechanisms that work above or "Epi" to the DNA itself. This includes: DNA methylation, histone modification, and Chromatin relaxation and access.

(F) (Nrf2) Signaling Pathway:

(G) (PPAR-γ)

(H) (SIRT1) Signaling Pathway:

(I) (AMPK) pathway.

(J) (Ion Channels) Regulation:
ion channels and transporters, including TRPV5, ROMK1, and the Na+/K+-ATPase pump.

(K) (MAPK/ERK) pathway.
Downregulation of phosphate reabsorption and vitamin D synthesis in the kidney, thus maintaining their homeostasis.

(L) (mTOR): Molecular Target of Rapamycin

(M) (NF-Kb)

(N) (Wnt) Signaling Pathway:

(O) (Antioxidant) Pathways or processes including: SOD; Catalase Pathway; Peroxiredoxin System, Peroxiredoxins (Prxs); Thioredoxin System, thioredoxin (Trx), thioredoxin reductase (TrxR), and NADPH.

(P) (Wildcard):
If the Target-Agent is associated with modulating a signaling pathway not listed above please include any and all you identify not previously listed above.

Age Controlling Pathways:
(Q) Sirt6

Sirtuins (1 through 6) regulate vital cellular processes by interacting with p53, Tert (telomerase), Klotho (KL), and FOXO1. These interactions suggest that sirtuin family members work with these four genes to regulate various cellular processes and maintain cellular homeostasis.

(R) FOXO1

FOXO1 is a forkhead box transcription factor family member and regulates cellular processes such as glucose metabolism, apoptosis, and stress response. SIRT1 deacetylates and activates FOXO1, increasing the expression of genes involved in gluconeogenesis and stress resistance. SIRT1 also interacts with and regulates the activity of other FOXO family members, including FOXO3 and FOXO4 (14,15).

(S) p53

TP53 is a tumor-suppressing gene that regulates cell growth, differentiation, and apoptosis. SIRT1, the best-studied member of the sirtuin family, has been shown to interact with p53 in response to DNA damage and to regulate TP53-dependent transcriptional activity. SIRT1 deacetylates p53, leading to reduced p53 activity and decreased expression of p53 target genes that have a role in apoptosis and cell cycle arrest (12).

(T) TERT

TERT gene and sirtuins as they interact with each other and modulate each other's activity and function. For example, SIRT1 can deacetylate the TERT gene and increase its expression. The TERT gene can also activate SIRT1 by inhibiting p53 signaling (16). In addition, SIRT1 and the TERT gene can cooperate to improve cellular senescence, stem cell function, and tumorigenesis. SIRT3 also deacetylates the TERT gene and increases its expression and activity (17). Conversely, SIRT3 can be activated by the TERT gene by inhibiting ROS production. Furthermore, SIRT3 and the TERT gene can cooperate to protect against mitochondrial dysfunction, oxidative stress, and apoptosis. SIRT6 deacetylates the TERT gene and decreases its expression and activity (18). The TERT gene can also inhibit SIRT6 through the activation of NF-κB signaling. Moreover, SIRT6 and the TERT gene can antagonize each other in regulating cellular senescence, DNA damage response, and tumorigenesis.

Output Formatting

IMPORTANT!!! ~ Please provide a prominent title (HEADER) with the name of the Target-Agent in large, BOLD, HEADER-STYLE text."

Please maintain the same table formatting as all the previous prompt responses in this thread.

IMPROTANT: Please provide an output for every identified molecular pathway; (A through O) detailed above.

Column #1 = (1Q) Molecular Pathways A - T
Column #2 = (2Q) Primary Biological Function
Column #3 ~ (3Q) Modulation Direction
Column #4 ~ (4Q) Downstream Cascades
Column #5 ~ (5Q) Synergistic Agents
Column #6 ~ (6Q) Synergistic Agent Pathways

Response Key - Triggering Prompt Activation

Respond "Ready for Target-Agent?" and I will paste the Target-Agent name for you to analyze? Please remember the HEADER TITLE FORMATTING. Thank you!