BIO ACCENT

BAOJ HIV

Ruggiero Marco, BAOJ HIV 2017, 3: 02
3: 029

Editorial

A Novel Approach to Klotho Aimed at Delaying and Reversing Aging

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Significance of Work

Premature aging represents a serious problem for people living with HIV. Accelerated aging of the immune system- immunosenescence - is associated with earlier occurrences of aging-related diseases in HIV patients. The approach described in this Editorial represents a breakthrough that has the potential to revolutionize the field of aging in people living with HIV. The multi-pronged approach targeting the anti-aging gene Klotho is based on Microbiome Medicine involving relativistic time dilation and quantum entanglement at the DNA level. This approach may be relevant for all aging-related conditions.

Abstract

Reason

Premature aging represents a serious problem for people living with HIV. Accelerated aging of the immune system- immunosenescence - is associated with earlier occurrences of aging-related diseases in HIV patients. Here I describe a novel approach targeting the anti-aging gene Klotho which has the goal of delaying and reversing aging.

Methods

This novel approach is based on four factors which amplify each other in targeting Klotho expression and signaling: 1. Orally-available, microbiologically-enhanced, transcriptional factors known to increase Klotho expression. 2. Microbial enzymes which mimic the enzymatic function of circulating Klotho. 3. Microbiologically-enhanced chondroitin sulfate which potentiates the effects of Klotho transcriptional factors at the epigenetic and quantum levels. 4. Relativistic time dilation and biological quantum entanglement.

Results

Microbial enhancement of chondroitin sulfate leads to 1. Restauration of Klotho expression through a mechanism mimicking histone acetylation; 2. Induction of general and Klotho-specific relativistic time dilation; 3. Restauration of DNA quantum entanglement by enhancing the ability of the nucleic acid to retain, process and transmit information at the epigenetic and quantum levels.

Conclusion

The integrated, multi-pronged approach described in this paper, targeting Klotho expression and signaling, represents a novel method for counteracting premature aging in people living with HIV as well as a method for counteracting aging in the general population. Implementation of strategies based on principles of relativistic time dilation and quantum signaling to Klotho has the potential to revolutionize the fields of HIV/AIDS research and aging with wide-ranging consequences.

Key Words: HIV; AIDS; Aging; Klotho; Microbiome; Relativistic Time Dilation; Quantum Biology

Main Text

Premature aging represents a serious problem for people living with HIV. Accelerated aging of the immune system- immunosenescence - is associated with earlier occurrences of aging-related diseases in HIV patients. The mechanisms underlying premature senescence highlight the role of the immune system in aging [1], and indicate ways to fight aging in immune deficient patients as well as in healthy individuals. An

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Sub Date: December 11th, 2017, **Acc Date:** December 20th, 2017, **Pub Date:** December 20th, 2017.

Citation: Ruggiero Marco (2017) A Novel Approach to Klotho Aimed at Delaying and Reversing Aging. BAOJ HIV 3: 029.

approach that may prove useful in delaying and even reversing aging is represented by procedures targeting Klotho, an age-suppressing gene whose over expression leads to extended lifespan [2]. Oddly enough, a PubMed search for "Klotho and HIV" performed in December 2017, yielded only two results [3,4], one of which however corroborates the hypothesis that increasing Klotho expression may prove useful in preventing age-related morbidities [3].

Klotho is a transmembrane multifunctional protein; the large extracellular domain is homologous to the enzymes glycosidases and, once released into the extracellular space, is found in blood, urine, and cerebrospinal fluid where it works as a humeral mediator - hormone - counteracting age-associated conditions. The domain of Klotho that remains associated with the plasma membrane after shedding of the extracellular domain, forms a complex with the fibroblast growth factor receptor, and this de novo formed multi-protein complex constitutes a high-affinity binding site for Fibroblast Growth Factor 23 (FGF23) [2]. Since circulating Klotho counteracts aging, extends lifespan, and protects against age-associated morbidities [5], it is conceivable that strategies aimed at increasing Klotho expression and elevating its circulating level may prove useful in contexts as diverse as chronic HIV infection to aging of the general population. Here, I describe a novel integrated, multi-pronged approach aimed at the anti-aging gene Klotho that is based on Microbiome Medicine as well as on relativistic time dilation and quantum entanglement at the DNA level. Since Klotho is a complex protein with a peculiar folding that is responsible for its pleiotropic functions, simplistic approaches such as supplementing Klotho protein through the oral route are obviously not feasible and suggest the need for an integrated multi-pronged approach.

This novel approach is based on four factors that amplify each other in targeting Klotho expression and signaling:

1. Orally-available, microbiologically-enhanced, transcriptional factors known to increase Klotho expression. These are represented by D-alpha-tocopherol [6], and vitamin D receptor (VDR) agonists such as cholecalciferol [7] and lithocholic acid [8]. In our approach, D-alpha-tocopherol and cholecalciferol are non-covalently bound to oligosaccharides derived from microbial enhancement of chondroitin sulfate (see point #3 below). Such non-covalent binding facilitates the interaction between the ligands and their nuclear receptors as well as the interaction between receptors and other transcriptional factors such as, for example, between VDR and the retinoic acid receptor. Lithocholic acid, a non-calcemic ligand for VDR with a number of anti-aging properties [9], is a by-product of the metabolism of Kluyveromyces marxianus, one of the microbial components of this approach (see point #2 below). Combination of these factors leads to increased expression of endogenous, human Klotho through transcriptional activation.

2. Microbial enzymes mimicking the enzymatic function of circulating Klotho. Microbial strains pertaining to this approach are known to synthesize and release glycosidases whose functions are analogous to those of circulating Klotho. Among the microbial strains constituting this approach, I focus on two representative strains: Lacotbacillus plantarum and Kluyveromyces marxianus, each strain endowed with known anti-aging properties. Lactobacillus plantarum, among its properties, reduces inflammation [10]; fights cancer and stimulates the immune system [11]; fights oxidative stress associated with aging [12]; and produces glycosidases that replicate the mechanism of action of Klotho [13]. Kluyveromyces marxianus reduces local and systemic inflammation, helps reconstitute the healthy human microbiota in concert with the other microbial components of this approach, stimulates the function of monocytes, modulates dendritic cell function, favors endogenous production short-chain fatty acids and lithocholic acid, protects against oxidative stress, and produces glycosidases such as beta-galactosidase and glucanase [14,15]. The mechanism of action of these latter enzymes is analogous to that of Klotho. In short, the strains pertaining to our approach lead to microbial production of enzymes homologous to circulating Klotho, de facto transforming the gut in natural a bio-reactor for production of Klotho-like enzymes. They also enhance human Klotho expression through production of lithocholic that activates VDR. Self-assembly of Klotho-like enzymes in the supramolecular structures described in a recent paper [16], is responsible for absorption of microbiologically-derived Klotho-like enzymes.

3. Microbiologically-enhanced chondroitin sulfate. Chondroitin sulfate is a glycosaminoglycan endowed with a number of healthy properties ranging from anti-aging to immune modulation and neuroprotection [14]. Supplements based on a chondroitin sulfate backbone have proven useful in conditions as diverse as cancer, autism, chronic and acute pain, inflammatory bowel disease and autoimmune kidney disease [17]. In the novel approach described here, the healthy gut microbiota, reconstituted as described above, metabolizes chondroitin sulfate leading to formation of oligosaccharides, mainly, but not uniquely, represented by disaccharides composed of glucuronic acid and N-acetylgalactosamine; these disaccharides in turn influence the function of the microbiota with profound, positive, effects ranging from immunomodulation to decreased inflammation and increased resistance to stressors [18,19]. Disaccharides of chondroitin sulfate, are internalized in cells and bind DNA through electrostatic interactions with DNA-binding proteins [20-22]. In particular, they interact with the histone core of the nucleosome of poorly acetylated (and hence poorly expressed) genes as it is the case for Klotho in aging and cancer [23]. Glucuronic acid binds to the non-acetylated lysine of the histone core of the nucleosome via acid-base interaction; such an interaction enhances gene expression with an epigenetic mechanism similar to that of physiological acetylation of histones. Binding of

glucuronic acid to histone, therefore, yields results comparable to those obtained with deacetylase inhibitors. The basic moiety of the disaccharide, N-acetylgalactosamine, binds to the deoxyribonucleic acid in a non-site-specific manner, further potentiating the ability of the molecular complex to enhance Klotho gene expression. In other words, disaccharides derived from microbial metabolism, that is, from the enhancement of chondroitin sulfate, restore the expression of Klotho and other critical genes, thus reproducing the results observed with histone deacetylase inhibitors used as drugs, with a long story of success in age-related morbidities involving psychiatry, neurology, cancer and inflammatory diseases [23].

4. Relativistic time dilation and biological quantum entanglement. As described in a recent paper [22], binding of chondroitin sulfate to DNA induces relativistic time dilation. Specific binding of microbiologically-enhanced chondroitin sulfate to non-acetylated Klotho leads to gene-specific relativistic time dilation that, in turn, provides increased time to regulate gene expression. This type of relativistic enhancement would substitute for the need of using histone deacetylase inhibitors with obvious advantages. In addition to relativistic time dilation, gene-specific binding of chondroitin sulfate disaccharides yields other interesting effects in the field of quantum biology. Quantum biology represents a fascinating and novel field where the effects of quantum physics are observed in biological processes ranging from human consciousness to photosynthesis, bird navigation and DNA function [25-28]. In the context of the novel approach described here, quantum entanglement between the electron clouds of nucleic acids is of particular interest for its implications in the ability of DNA to retain, process and transmit information [28].

The concept of quantum-based information in DNA derives from the observation that DNA has the properties of a fractal antenna able to receive and send signals under the form of electromagnetic waves where, by definition, quantum processes are at work [29]. Interaction of highly charged disaccharides and their electron clouds with the multi-molecular structure constituted by DNA and proteins modifies the quantum properties of DNA enhancing its ability to retain, process and transmit information that is entangled at quantum level; as far as Klotho is concerned, quantum-based mechanisms add to the restauration of epigenetic information through transcriptional activation as described above. Restauration of Klotho expression may lead to other significant consequences as the role of Klotho in carcinogenesis, tumor progression, and cancer prognosis is becoming more evident. Such a role of Klotho in cancer is so important that it is being described as a tumor suppressor since it inhibits insulin/IGF1, p53/p21, and Wnt signaling [30]. Restauration of Klotho expression is also relevant in protecting cells of the immune system against the effects of lipopolysaccharide (LPS) of Gram-negative bacteria, thus contributing to the efficacy of the immune system in the context of immunotherapy; LPS is known to induce senescence in monocytes, and Klotho protects monocytes from LPS-induced damage by reducing oxidative stress, favoring DNA repair and restoring the cells' immune functions [31].

As far as aging and immune system function are concerned, it is worth noticing that premature aging in HIV/AIDS is different in many aspects from physiological aging as it is the results of the interplay of biological events, toxic events, and therapeutic side effects where other anti-aging genes, in addition to Klotho, are involved. For example, it has been demonstrated that anti-retroviral drugs such as nucleoside reverse transcriptase inhibitors, inhibit telomerase activity with consequent telomere shortening, thus suggesting that telomerase is involved in the pathogenesis of premature aging in HIV/AIDS [32]. Likewise, the role of another class of aging-related proteins, sirtuins, in HIV-infected patients is rather peculiar and different from that in healthy individuals. Sirtuins are a family of NAD+-dependent enzymes endowed with deacetylase activity; they regulate cell survival, energy metabolism, and are involved in inflammation, cancer and HIV replication. In particular, Sirtuin-1 (SIRT1) de-acetylates the HIV-1 Tat protein catalyzing a fundamental step to start new cycles of viral transcription [33]. In other words, at variance with other models where sirtuins appear to have anti-aging effects [34], their role in HIV is more complex and may indirectly lead to HIV-associated senescence. However, in healthy individuals, the anti-aging pathways of sirtuins and Klotho appear to be interconnected as demonstrated by the effects of resveratrol, a natural polyphenol endowed with anti-aging properties both in vivo and in vitro; resveratrol induces the expression of Klotho through activating transcription factor 3 (ATF3) and c-Jun signaling, and also enhances the expression of SIRT1 [35]. In the context of the mechanisms described in this paper, it can be hypothesized that binding of glucuronic acid to the lysine residues of histones pertaining to the gene coding for SIRT1 leads to increased expression of this sirtuin with notable consequences such as, for example, enhancing the survival of human embryonic stem cells by promoting DNA repair, thus contributing to the development of safe and effective cell therapies [36].

Conclusion

Microbial enhancement of chondroitin sulfate leads to restauration of Klotho expression through a mechanism mimicking histone acetylation; induces general and Klotho-specific relativistic time dilation; restores DNA quantum entanglement and enhances the ability of the nucleic acid to retain, process and transmit information at the epigenetic and quantum levels.

The integrated, multi-pronged approach targeting Klotho expression and signaling, represents a novel method for counteracting premature aging in people living with HIV as well as a method for counteracting aging in the general population. Implementation of strategies based on principles of relativistic time dilation and quantum signaling to Klotho has the potential to revolutionize the fields of HIV/AIDS research and aging with wide-ranging consequences.

Competing Interests

Marco Ruggiero is the founder and CEO of Silver Spring, a Swiss research and development company in the field of supplements and probiotics. No products of Silver Spring are mentioned in this study. Marco Ruggiero is the inventor of the immune stimulating molecule designated Rerum® mentioned in reference n. 17.

Author's Contribution

Marco Ruggiero developed the concepts and the approach described in this paper and wrote the manuscript.

Acknowledgements

The Author wishes to thank Dr. Jerry Blythe, MD, for critical review of the manuscript and for providing precious suggestions.

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