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[Commentary] Interconnected Pathways of Albumin, Insulin, Metformin, and the Klotho Protein: Unveiling their Synergistic Roles as Anti-Aging Agents

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Funding: No specific funding was received for this work.

Potential competing interests: No potential competing interests to declare.

Abstract

This manuscript delves into the potential of insulin sensitizers, specifically Metformin and GLP1 with Degludec, as anti-aging agents, focusing on the multifaceted functions of albumin and its association with age-related changes.

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Keywords: insulin sensitizers, Metformin, GLP1 with Degludec, albumin, aging, protein homeostasis, insulin signaling, healthy aging, anti-aging agents, protein aggregation, lifespan extension, cognitive function, therapeutic strategies, personalized interventions.

Albumin, the predominant protein found in human blood plasma, plays a pivotal role in the transportation of substances throughout the bloodstream. However, its functions go beyond mere transportation, encompassing tasks such as hydrogen ion binding, hormone transport, toxin neutralization, and drug distribution. [1] Recognizing the significance of these functions, maintaining consistent albumin levels throughout life becomes imperative to counteract the adverse effects of aging. Recent research has unveiled a correlation between declining albumin levels and the aging process. In particular, a 2022 study identified circulating albumin as the most important biomarker in predicting an individual's

biological age, surpassing even glucose levels in significance. [2] Another study in 2019 demonstrated the vital role of maintaining albumin levels in preserving neurological health. [3] Disruptions in the blood-brain barrier, associated with albumin deficiency, were found to lead to cognitive impairment and neurological aging in mice.

Despite the critical role of albumin and its age-related decline, current medical understanding categorizes this decline as a natural and unavoidable process. [4] However, as more studies emphasize the importance of albumin, this perception may change. It is crucial for individuals to be aware of the multifaceted functions of albumin and to challenge the assumption that decreasing levels are inconsequential in the context of aging. [5] Additionally, extensive research on diabetes, characterized by dysregulated glucose, lipid, and protein metabolism, has revealed its connection to albumin production. [6] Insulin, a key regulator of glucose and lipid metabolism, has been found to influence albumin gene expression. Disruption of insulin signaling in mice led to decreased albumin secretion, a decrease that was rescued by the deletion of Forkhead Box O1 (Foxo1). These findings highlight the intricate connection between insulin and albumin, with Foxo1 acting as a repressor of albumin expression. [7]

Furthermore, investigations into the interaction between Human Serum Albumin (HSA) and native human insulin and its fragments have demonstrated HSA's ability to inhibit their aggregation. Samples containing native insulin or its fragments exhibited the formation of amyloid structures, while HSA complexes displayed distinct secondary structures. [8] These results underscore the importance of albumin in maintaining protein homeostasis by preventing aggregation. A groundbreaking experiment involved the delivery of unmodified serum albumin to middle-aged mice, diluting the presence of damaged albumin and reversing the detrimental responses to pro-aging signals in the blood. This intervention resulted in a significant increase in lifespan, with female mice experiencing a 17.6% extension and male mice a 20.3% extension. Additionally, the treated mice displayed improved physical capabilities, including increased grip strength and enhanced performance in cognitive tests. [9]

Insulin, a hormone crucial for glucose regulation, exhibits a high affinity for its receptors.[10] This binding affinity enables precise signaling and efficient glucose uptake by cells. Insulin sensitizers, such as degludec and GLP-1 analogs like semaglutide, also demonstrate a strong affinity for albumin, a major plasma protein. [11] Albumin, as a carrier protein, plays a vital role in the transport of various substances, including drugs. [12] Metformin, an oral antidiabetic medication, binds to albumin within the plasma. This interaction influences the pharmacokinetics and pharmacodynamics of metformin. The binding mechanism between metformin and albumin involves non-covalent interactions, primarily driven by hydrophobic and electrostatic forces. [13] These interactions prolong the half-life of metformin, enhance its distribution, and impact its bioavailability. [14] Metformin's binding to albumin also contributes to its mTOR inhibitory effect.[15] The mTOR pathway regulates cellular growth, metabolism, and aging. By inhibiting mTOR signaling, metformin has the potential to modulate aging-related processes. [16] In addition, degludec, a long-acting insulin analog, has been investigated for its effects on interleukin-6 (IL-6), a pro-inflammatory cytokine associated with insulin resistance and chronic inflammation. Degludec has shown potential in reducing IL-6 levels, suggesting its anti-inflammatory properties and potential benefits in managing insulin resistance. [17]

The Klotho protein plays a crucial role as an anti-aging factor in various biological processes. Its involvement in extending

lifespan has attracted significant attention from researchers. This protein exerts its effects through intricate mechanisms that contribute to the regulation of aging. [18] One mechanism by which the Klotho protein influences lifespan extension is through its impact on insulin and insulin-like growth factor-1 (IGF-1) signaling pathways. Klotho protein enhances insulin sensitivity and attenuates IGF-1 signaling, leading to a reduction in the activity of the mammalian target of rapamycin (mTOR) pathway. The mTOR pathway is involved in regulating cellular metabolism and growth. By inhibiting mTOR signaling, Klotho protein helps to maintain cellular homeostasis and promotes longevity. [19]

Furthermore, the Klotho protein modulates oxidative stress and inflammation, both of which are key contributors to aging. It acts as a potent antioxidant by reducing the production of reactive oxygen species (ROS) and enhancing the activity of antioxidant enzymes. Additionally, Klotho protein suppresses pro-inflammatory signaling pathways, thereby reducing chronic inflammation associated with aging. [20] GLP-1 (Glucagon-like peptide-1) plays a pivotal role in increasing and activating the Klotho protein. GLP-1 is a hormone secreted by the intestines in response to food intake. It acts on the GLP-1 receptor, which is expressed in various tissues including the brain, pancreas, and kidneys. Activation of the GLP-1 receptor stimulates the production and release of the Klotho protein. [21]

The mechanism by which GLP-1 enhances Klotho protein levels involves the activation of protein kinase A (PKA) and protein kinase C (PKC) signaling pathways. These pathways ultimately lead to the upregulation of Klotho gene expression and increased synthesis of the Klotho protein. Consequently, the elevation of GLP-1 levels through various interventions such as GLP-1 receptor agonists or inhibitors of GLP-1 degradation can effectively boost Klotho protein levels and potentially promote anti-aging effects. [22] Moving on to the role of metformin in increasing Klotho protein levels, metformin is a widely used medication for the management of type 2 diabetes. Studies have shown that metformin can upregulate Klotho expression and enhance Klotho protein levels. The precise mechanism underlying this effect is not fully understood, but it is believed to involve the activation of adenosine monophosphate-activated protein kinase (AMPK) signaling pathway.

Activation of AMPK by metformin leads to the phosphorylation of transcription factors that regulate Klotho gene expression, resulting in increased Klotho protein production. [23] SGLT2 inhibitors (SGLT2i) are a class of medications commonly used in the treatment of type 2 diabetes. Recent studies have shown that SGLT2i therapy leads to a notable increase in the levels of a protein called Klotho in both the bloodstream (serum) and urine. This increase in Klotho expression is observed across different SGLT2 inhibitors, suggesting that it is a class effect rather than specific to individual medications within the class. Klotho is known to have various beneficial effects on health, including potential roles in cardiovascular protection and anti-aging processes. The preservation of Klotho expression through SGLT2i therapy highlights a potential mechanism by which these medications may contribute to their therapeutic effects beyond glycemic control in patients with type 2 diabetes. [24]

Finally, the association between Klotho protein and albumin (a major protein in the blood) has been investigated. It has been observed that Klotho protein binds to albumin, forming a complex that circulates in the bloodstream. This interaction between Klotho protein and albumin may have implications for the transport and distribution of Klotho protein in the body. However, further research is needed to fully elucidate the functional significance of this association. [25]

In summary, this extensive exploration into the roles of albumin, insulin, and the Klotho protein has illuminated a complex network of molecular interactions with profound implications for aging and health. Albumin, beyond its conventional function in substance transportation, emerges as a critical player in neurological health, cognitive function, and as a potential biomarker for biological age. The age-related decline in albumin levels, once considered a natural process, is now viewed through a lens that underscores its significance, prompting a reassessment of its implications in the context of aging. The intricate connection between insulin and albumin further amplifies the multifaceted nature of these interactions, revealing the delicate balance required for maintaining optimal physiological functioning. Insights from studies on insulin signaling disruptions, albumin's role in preventing protein aggregation, and the groundbreaking experiment involving serum albumin delivery to middle-aged mice collectively suggest avenues for intervention to counteract pro-aging signals and extend lifespan. In parallel, the discussion extends to the pharmacological realm, where the interplay between albumin and medications like metformin, insulin sensitizers, and SGLT2 inhibitors introduces novel perspectives. Beyond glycemic control, these medications exhibit intricate connections with albumin, influencing drug pharmacokinetics, mTOR signaling, and anti-inflammatory responses. Particularly noteworthy is the potential of metformin and SGLT2 inhibitors in upregulating Klotho protein expression, revealing a link between diabetes management and anti-aging effects, shedding light on mechanisms that extend beyond their primary therapeutic goals. The anti-aging prowess of the Klotho protein is underscored through its regulatory impact on insulin and IGF-1 signaling, mTOR pathway modulation, and its role in combating oxidative stress and inflammation. GLP-1's ability to enhance Klotho protein levels introduces a promising avenue for interventions aimed at promoting anti-aging effects. However, the association between Klotho protein and albumin, forming a circulating complex, introduces a yet-to-be-fully-explored dimension. While intriguing, its functional significance requires further elucidation through continued research.

In conclusion, the amalgamation of these findings suggests a comprehensive approach to anti-aging interventions. Recognizing the pivotal roles of albumin, insulin, and the Klotho protein opens avenues for targeted therapeutic strategies that extend beyond conventional paradigms, providing a foundation for future research aimed at promoting healthy aging and longevity.

Statements and Declarations

The authors declare that there are no conflicts of interest.

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