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Cell & Cellular Life Sciences Journal
ISSN: 2578-4811

Unveiling the Interplay of Klotho Protein, Chemotherapy-Induced Klotho Protein Deficiency and the Pivotal Role of GLP-1 Agonists like Ozempic in Cancer Survivorship Patient Survival Rate after Chemotherapy Treatment

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Letter to Editor

Volume 9 Issue 1

Received Date: December 29, 2023

Published Date: January 10, 2024

DOI: 10.23880/cclsj-16000193

Abstract

Cancer, a pervasive health challenge globally, prompts aggressive treatment measures, with chemotherapy as a primary approach targeting uncontrolled cell growth. While effective against tumors, chemotherapeutic agents, especially alkylating agents, antimetabolites, and other classes, introduce collateral damage to healthy tissues, notably the kidneys. This article explores the intricate impact of chemotherapy on renal proteins and enzymes, particularly the Klotho protein, a key player in aging and longevity. Alkylating agents induce renal toxicity through oxidative stress, affecting Klotho synthesis and antioxidant defenses. Antimetabolites disrupt DNA synthesis, potentially impairing renal function. Antitumor antibiotics, topoisomerase inhibitors, mitotic inhibitors, and hormone therapies each contribute to nephrotoxicity. As Klotho deficiency emerges as a critical factor in the shortened lifespan of cancer patients, the potential role of GLP-1 agonists like Ozempic in stimulating Klotho production is discussed. This dual-action approach could mitigate chemotherapy-induced nephrotoxicity, offering a novel strategy for enhancing the well-being and lifespan of cancer patients.

Keywords: Chemotherapy; Nephrotoxicity; Renal Proteins; Klotho Protein; Alkylating Agents; Antimetabolites; Glp-1 Agonists; Ozempic; Cancer Longevity

Abbreviations: ROS: Reactive Oxygen Species; MTOR: Mammalian Target of Rapamycin; GF: Growth Factor; GLP: Glucagon-Like Peptide; PKA: Protein Kinase; A CAMP: Cyclic Adenosine Monophosphate.

Letter to Editor

Cancer, a complex and multifaceted group of diseases characterized by uncontrolled cell growth and proliferation, poses a significant health challenge globally. Chemotherapy stands out as a cornerstone in the treatment of various cancers, aiming to inhibit the rapid division of malignant cells [1]. One prominent category of chemotherapeutic agents is alkylating agents, exemplified by Cyclophosphamide, cisplatin, and temozolomide. These agents damage DNA by introducing alkyl groups, thereby disrupting the DNA structure and impeding cell division [2]. Antimetabolites, such as Methotrexate, 5-fluorouracil, and gemcitabine, represent

another vital class of chemotherapeutic drugs. Operating by mimicking or interfering with essential substances required for DNA synthesis, they effectively inhibit cell division. Additionally, antitumor antibiotics, including Doxorubicin and bleomycin, disrupt DNA replication and RNA synthesis, causing DNA strand breaks and preventing cell division [3].

Topoisomerase inhibitors, exemplified by Topotecan and Irinotecan, interfere with enzymes crucial for DNA replication, inducing DNA damage and inhibiting cell growth. Mitotic inhibitors, such as Paclitaxel and vincristine, disrupt the mitotic spindle apparatus, hindering proper cell division. Hormone therapy, illustrated by Tamoxifen for breast cancer and leuprolide for prostate cancer, targets hormones that fuel specific tumor types, effectively inhibiting their growth [4]. Moreover, targeted therapies like Imatinib and trastuzumab focus on specific molecules involved in cancer cell growth, minimizing damage to healthy cells. Immunotherapy, represented by checkpoint inhibitors like pembrolizumab and CAR-T cell therapy, boosts the body's immune system to recognize and destroy cancer cells [5].

While these treatments exhibit efficacy against tumors, their impact on kidney function, particularly in the synthesis of the Klotho protein, warrants consideration; Chemotherapy-Induced Nephrotoxicity: Unraveling the Intricate Impact on Renal Proteins and Enzymes. The intricate mechanisms underlying chemotherapy-induced nephrotoxicity involve a cascade of events that impact various proteins, enzymes, and renal functions [6]. Alkylating Agents: Cyclophosphamide, cisplatin, and temozolomide, prominent alkylating agents, induce renal toxicity by generating reactive oxygen species (ROS) and oxidative stress.

These agents disrupt the delicate equilibrium required for efficient Klotho synthesis, affecting its anti-aging properties. Additionally, they impair glutathione peroxidase, a crucial antioxidant enzyme, leading to increased oxidative stress within the kidneys. Antimetabolites: Methotrexate, 5-fluorouracil, and gemcitabine, as antimetabolites, interfere with DNA synthesis, affecting rapidly dividing cells. However, their impact on renal function involves the inhibition of dihydrofolate reductase, essential for folate metabolism, resulting in impaired DNA synthesis within renal cells and potential nephrotoxicity [7].

- **Antitumor Antibiotics:** Doxorubicin and bleomycin, antitumor antibiotics, interfere with DNA replication. Doxorubicin, known for its cardiotoxicity, also induces nephrotoxicity by inhibiting topoisomerase II, leading to DNA damage and impairment of renal cells. Bleomycin exacerbates oxidative stress, adversely affecting renal antioxidant defences [8].
- **Topoisomerase Inhibitors:** Topotecan and irinotecan, topoisomerase inhibitors, induce nephrotoxicity through the inhibition of enzymes crucial for DNA replication. This disruption results in DNA damage within renal cells, impacting their ability to maintain normal physiological functions [9].
- **Mitotic Inhibitors:** Paclitaxel and vincristine, mitotic inhibitors, disrupt microtubules, crucial for proper cell division. These agents, while effective against cancer, can lead to tubular cell injury and affect renal filtration processes [10].
- **Hormone Therapy:** Tamoxifen and leuprolide, examples of hormone therapy, impact hormonal balance. Tamoxifen's metabolites may contribute to renal toxicity, affecting proximal tubular function. Leuprolide, used in prostate cancer, can influence fluid and electrolyte balance, impacting renal homeostasis [11].
- **Targeted Therapies and Immunotherapy:** Imatinib, trastuzumab, and immunotherapies like pembrolizumab may cause renal side effects. Imatinib affects podocytes, crucial for glomerular function, while trastuzumab is associated with proteinuria. Immunotherapies may lead to immune-mediated nephrotoxicity [12].

The Klotho protein, named after the Greek fate responsible for spinning the thread of life, has emerged as a pivotal player in the intricate tapestry of aging and longevity. Extensively studied for its multifaceted roles, Klotho stands at the crossroads of cellular and physiological processes that collectively contribute to increased lifespan and the attenuation of age-related degeneration [13]. At a foundational level, Klotho is recognized for its ability to modulate various signalling pathways, notably those associated with insulin and insulin-like growth factor-1 (IGF-1). By enhancing insulin sensitivity and dampening IGF-1 signalling, Klotho exerts a regulatory influence on the mammalian target of rapamycin (mTOR) pathway. This signalling cascade plays a central role in cellular metabolism and growth, and Klotho's inhibitory effect on mTOR contributes to the maintenance of cellular homeostasis, thus promoting longevity [14]. The impact of Klotho extends beyond the molecular realm to the realm of oxidative stress and inflammation, key contributors to the aging process. Functioning as a potent antioxidant, Klotho reduces the production of reactive oxygen species (ROS) and enhances the activity of antioxidant enzymes [15].

Simultaneously, Klotho acts as a suppressor of pro-inflammatory signalling pathways, mitigating chronic inflammation associated with aging. This dual role in mitigating oxidative stress and dampening inflammatory responses underscores its comprehensive anti-aging properties [16]. Chemotherapy, a potent weapon in the fight against cancer, can inadvertently unleash collateral damage on healthy tissues, particularly the kidneys, leading to a phenomenon known as nephrotoxicity. This renal toxicity

can significantly impact the intricate processes involved in the synthesis of the Klotho protein.

The nephrotoxic effects of chemotherapeutic agents, such as alkylating agents and antimetabolites, create a hostile microenvironment within the kidneys [17]. The production of reactive oxygen species (ROS) and oxidative stress induced by these agents disrupts the delicate balance required for efficient Klotho synthesis. Moreover, the interference with cellular mechanisms involved in Klotho production, including transcription and translation processes, further compounds the decline in Klotho levels. As a result, cancer patients undergoing chemotherapy experience a notable reduction in Klotho protein production, setting the stage for potential repercussions on aging-related processes and overall health.

The deficiency in Klotho protein synthesis among cancer patients emerges as a pivotal contributor to the shortened lifespan observed in this cohort. Klotho, recognized for its multifaceted roles in cellular homeostasis and anti-aging processes, plays a crucial part in regulating various signalling pathways associated with insulin, insulin-like growth factor-1 (IGF-1), and the mammalian target of rapamycin (mTOR). As cancer patients undergo chemotherapy, a cornerstone in cancer treatment, the collateral damage inflicted on healthy tissues, particularly the kidneys, can result in nephrotoxicity. This renal toxicity disrupts the delicate equilibrium necessary for efficient Klotho synthesis [18,19].

The consequences of diminished Klotho extend to its regulatory effects on aging-related processes. Klotho's ability to modulate insulin sensitivity, dampen IGF-1 signalling, and inhibit the mTOR pathway positions it as a key player in cellular homeostasis and longevity. Therefore, the chemotherapy-induced shortfall in Klotho production becomes a critical factor in the observed decline in lifespan among cancer patients [20].

The role of glucagon-like peptide-1 (GLP-1) agonists, such as Ozempic, in stimulating Klotho protein production presents a promising avenue for extending the lifespan of cancer patients. GLP-1, a hormone released in response to food intake, not only regulates glucose metabolism but also influences various physiological processes. Semaglutide, the active component of Ozempic, engages with GLP-1 receptors, particularly expressed in the pancreas, brain, and kidneys. This interaction initiates a complex intracellular cascade involving protein kinase A (PKA) and protein kinase C (PKC) [21]. By binding to GLP-1 receptors, semaglutide activates adenylate cyclase, leading to an elevation in cyclic adenosine monophosphate (cAMP) levels. This increase in cAMP activates PKA, a central signaling molecule that, in turn, phosphorylates transcription factors associated with the GLP-1 gene. Simultaneously, semaglutide induces the activation of PKC, contributing to the upregulation of the GLP-1 gene [22].

The stimulation of GLP-1 production by semaglutide triggers the release of GLP-1 into the bloodstream, influencing not only glucose homeostasis but also potential anti-inflammatory and cardiovascular benefits [23]. Moreover, scientific studies have shown that GLP-1 agonists, including semaglutide, can upregulate the expression of the Klotho gene. Klotho, recognized for its pivotal role in anti-aging processes and cellular homeostasis, is prominently expressed in the kidneys. The potential of GLP-1 agonists to stimulate Klotho production introduces a novel perspective in cancer treatment. Given that chemotherapy often leads to Klotho deficiency, utilizing GLP-1 agonists as stimulants for Klotho synthesis offers a dual benefit. Not only can this approach mitigate the adverse effects of chemotherapy on renal function and Klotho levels, but it also presents a potential avenue for enhancing the overall well-being and lifespan of cancer patients [24-26].

As ongoing research delves deeper into the intricate interplay between GLP-1 stimulation, Klotho protein expression, and their collective impact on health, the prospect of incorporating GLP-1 agonists into cancer treatment regimens emerges as a promising strategy. Guiding Dosage and Clinical Considerations: Precision in determining the exenatide dosage for preventive interventions necessitates a careful equilibrium between effectiveness and safety. Clinical trials exploring exenatide's preventive capabilities against diabetes commonly initiate with a standardized dose, typically 0.5 mg administered once weekly, allowing subsequent adjustments based on individual responses. This refined methodology aligns with the fundamental principle of mirroring physiological GLP-1 levels, aiming to optimize therapeutic advantages while minimizing potential side effects [27]. Moreover, leveraging a guiding dose of Ozempic, a representative GLP-1 agonist, could serve as a potential strategy to activate and stimulate Klotho protein production after or concurrently with chemotherapy. This approach is proposed as a plausible means to extend the lifespan of cancer patients, emphasizing the promising role of GLP-1 agonists in conjunction with chemotherapy.

In conclusion, the delicate balance between cancer treatment, renal health, and the Klotho protein unveils a multifaceted landscape that requires nuanced consideration. As we navigate these complexities, optimizing therapeutic strategies becomes imperative not only for combatting cancer but also for preserving the intricate tapestry of aging and longevity. Recognizing the pivotal role of Klotho in this narrative opens avenues for innovative interventions, offering hope for extended lifespans and improved well-being for those traversing the challenging terrain of cancer

and its treatments.

Statements and Declarations

The authors declare that there are no conflicts of interest.

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