BJCMR Brazilian Journal of Clinical Medicine and Review

PCAA PUBLICAÇÕES CIENTÍFICAS DE ACESSO ABERTO

Medical Hypotesis

Is Klotho Gene a Biomarker to Pathogenesis of Myelodysplastic Syndrome in Elderly Patient? A New Hypothesis

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Abstract: An important new biomarker for cancer is the Klotho, an anti-aging target, associated to proliferation and apoptosis of tumor cells. In this study, we hypothesized that the Myelodysplastic syndrome (MDS) pathogenesis, an elderly hematopoietic disease, can be affect by block of the Klotho expression, increasing ROS production in the medullary microenvironment, attenuating the DNA damage in HSCs, and leading to reduced count of blood cell precursors, characterizing the cytopenic profile of MDS patient. The absence or negative regulation of Klotho may be a poor prognostic marker of MDS, especially when patients are stratified by age. We believed that younger adult MDS patients show a higher Klotho expression while compared to old adults MDS patients, demonstrating that its expression is decreased with increasing age, representing a more aggressive disease. To confirm this hypothesis, an extensive clinical case-control study can be performed on bone marrow cell samples of MDS patients to show differential expression of Klotho gene and protein, and as this target can be modulate in this disease (based on promoter region methylation analysis). These approaches may define the Klotho as a new pathologic marker to MDS in elderly and improve future potential therapies.

Keywords: Klotho; Aging; Myelodysplastic syndrome; Biomarkers.

Citation: Góes JVC, Ribeiro-Junior HL. Is Klotho Gene a Biomarker to Pathogenesis of Myelodysplastic Syndrome in Elderly Patient? A New Hypothesis. Brazilian Journal of Clinical Medicine and Review. 2023 Jan-Mar;01(1):3-6.

Received: 1 January 2023
Accepted: 25 January 2023
Published: 29 January 2023

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1. Introduction

Myelodysplastic syndrome (MDS) is a disease of the hematopoietic stem-cells (HSCs) characterized by a multiple-step pathogenesis and an ineffective hematopoiesis [1], increased of medullar apoptosis [2], with high potential of malignancy and clonal evolution for acute myeloid leukemia (AML) [3]. The MDS incidence around the world is 5/100.000. In elderly, these values increase to 22–45/100.000 among subjects aged > 70 years and continues to increase with advancing age [4], thus making it the most frequent hematological disease in the older people.

An important explanation for the occurrence of MDS in the elderly is associated with the quiescence of HSCs [5-6]. The most recent hypothesis to this point is proposed by Mattiucci and colleagues [5] when related that the aging and senescence is related to alterations in mesenchymal stromal cells in MDS. The authors showed that during aging, the different subtypes of HSCs lose the ability to differentiate into lymphoid and myeloid precursor cells, causing a breakdown in the balance of the immune system [5-6]. This process exposes HSCs to important genotoxic factors (i.e. oxygen concentration, cytokines, and hormones) and may induce genetic or epigenetic alterations, because exposure to reactive oxygen species (ROS), increasing the risk of hematological malignancies [5, 7]. ROS mediate growth factor signaling can contribute to malignant phenotypes, by stimulating

cell growth and proliferation, promoting genetic instability, and helping evade senescence [8]. Interestingly, chromosomal abnormalities promoted by genomic instability are important findings in MDS diagnosis and in the establishment of patient's prognosis risk score [3].

An important new biomarker for cancer is the Klotho, a gene expressed mainly in renal distal convoluted tubules and brain choroid plexus and is associated to extending life span [9]. Dysregulation of Klotho was related to the proliferation and apoptosis of tumor cells [9]. Murine studies showed that Klotho deficiency developed aging features, such as short survival, skin atrophy, osteoporosis, and arteriosclerosis [10]. Also, Klotho is a co-receptor for endocrine fibroblast growth factor (FGF signaling, especially the FGF-23), an important proto-oncogene often activates in several human cancers [10].

Recently, Ji et al. [11], in a murine model, associated higher Klotho expression (mRNA and protein) with a decreased production of ROS in the brain and kidney tissues, extending the animal life span, when associated to aerobic exercise. This finding makes an important link to a possible association between increased expression of Klotho and the decreased of the effects caused by ROS produced by the aging of HSCs, a feature of ineffective hematopoiesis in elderly. However, this association is not clearly explained.

Based on topic, Mao and colleagues [12] demonstrated that various studies related Klotho expression with carcinogenesis. However, the association of Klotho expression in hematological diseases remains unclear.

2. Role of Klotho in the control of hematopoiesis and hematological malignances

Naturally, the hematopoiesis process is affected by aging, whether in human or mice. Aging process is associated with disruption of normal hematopoiesis resulting in an increase in the prevalence of anemia [13-14], the main feature of MDS [1]. It is known that Klotho functions, as an aging suppressor gene in mammals, and loss of Klotho are related to endothelial dysfunction by promote oxidative stress [10], affecting hematopoietic process by altering the medullary microenvironment [15].

In murine models, several studies demonstrated the role of Klotho in hematopoietic state, especially in stem cell development, erythropoiesis [13] or B lymphopoiesis [16]. Madathil et al. [13] related the in vivo role of Klotho genetic inactivation in the blood cell formation and differentiation. Klotho-/- mice showed a significant increase erythropoiesis and a decrease in the hematopoietic stem cell pool size in the bone marrow, leading to impaired hematopoietic stem cell homing in vivo [13].

On the other hand, Klotho-/- mice had an important decreased number of B lymphoid cells in BM and peripheral blood when compared to wild-type mice [16]. However, this group showed a normal number of myeloid cells count (i.e. erythroid lineage). Okada and collaborators [16] highlight that IL-7-responsive B cell precursors and all the maturation stages of B cells were also reduced. These results showed the role of Klotho protein to regulation of B lymphopoiesis in the hematopoietic cascade.

In human studies, Mao e colleagues [12] related the association between Klotho expression and cancer risk. Malignances with Klotho protein expression decreased odds ratio according to control group, with no difference between male or female patients [12]. The authors identified that overall cancer types (i.e., solid tumors in ovarian and esophageal) with Klotho protein expression showed a lower risk and progression of disease when compared to absence of Klotho expression tissue [12]. However, no associations with hematological malignances were identified in this study.

In hematological diseases, previous studies have demonstrated important associations of Klotho expression in T-cell lymphoma (TCL) [17] and diffuse large B-cell lymphoma (DLBCL) [18]. Initially, lower expression of Klotho gene was associated with T-cell lymphoma when compared to normal lymph nodes. In a second step, overexpression of Klotho inhibited tumor viability and promoted apoptosis in T cell lymphoma. Also, higher Klotho expression has declined IF-1R signaling activation [17].

Next, based on immunohistochemistry and western blotting analysis, lower expression level of Klotho was observed in DLBCL [18]. Also, similarly to T-cell lymphoma, up-regulation of Klotho protein induced cell apoptosis, inhibit tumor growth and declined activation of IGF-1R signaling in DLBCL. Thus, these results establish that inactivation of αKlotho is a tumor suppressor and modulator of IGF-1R in TCL and DLBCL [17-18]. Interestingly, the role of αKlotho, and β and γ subtypes, remains unclear in MDS, a disease characterized by failures in hematopoiesis.

3. Medical hypothesis and future perspectives

The MDS pathogenesis, an elderly hematopoietic disease, can be affect by block of the Klotho expression, increasing ROS production in the medullary microenvironment, attenuating the DNA damage in HSCs, and leading to reduced count of blood cell precursors, characterizing the cytopenic profile of MDS patient (Figure 1A). We hypothesized that absence or negative regulation of Klotho may be a poor prognostic marker of MDS, especially when patients are stratified by age (Figure 1B). We believed that younger adult MDS patients show a higher Klotho expression while compared to old adults MDS patients (Figure 1C), demonstrating that its expression is decreased with increasing age, representing a more aggressive disease [19].

To confirm this hypothesis, an extensive clinical case-control study can be performed on bone marrow cell samples of MDS patients to show differential expression of Klotho genes (i.e.. α, β and γ subtypes) and its proteins, showing as this target can be modulated in this disease (for example, based on promoter region methylation analysis). Also, Evaluation of the mutations in klotho gene by next-generation sequencing approaches in MDS progression cases may has the capacity to reveal the underlying molecular landscape and potentially provide targets for specific inhibitors to treatment of this disease. Thus, these approaches may define the Klotho as a new pathologic marker to Myelodysplastic syndrome in elderly and improve future potential therapies.

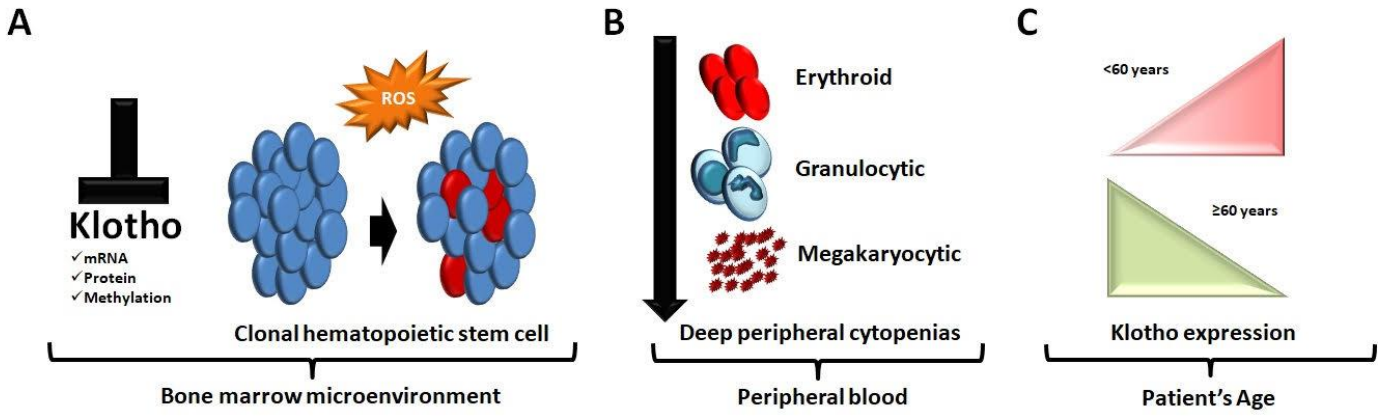

Figure 1: Klotho may be involved in pathogenesis of Myelodysplastic syndrome (MDS) in elderly individuals by promote oxidative stress (A), affecting hematopoiesis process in bone marrow hematopoietic stem cells (B), leading to deep peripheral cytopenias, a main feature of MDS.

Funding: None.

Research Ethics Committee Approval: None.

Acknowledgments: None.

Conflicts of Interest: The authors declare no conflict of interest.

Supplementary Materials: None.

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