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Klotho-HIV and Oxidative Stress: The Role of Klotho in Cardiovascular Disease Under HIV Infection—A Review

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Combined antiretroviral therapy has improved quality and life expectancy of people living with human immunodeficiency virus (HIV). However, this therapy increases oxidative stress (OS), which in turn causes alterations in lipid and carbon metabolism, kidney disease, liver cirrhosis, and increased risk of cardiovascular disease. The Klotho gene has been implicated in cardiovascular risk increase. Klotho protein expression at X level decreases the risk of heart disease. HIV-positive people usually present low plasma levels of Klotho; thus, contributing to some extent to an increase in cardiovascular risk for these types of patients, mostly by favoring atherosclerosis. Therefore, our aim is to provide an overview of the effect of OS on Klotho protein and its consequent cardiometabolic alterations in HIV-positive patients on antiretroviral therapy.

Keywords: reactive oxygen species, Klotho, cardiometabolic alteration, HIV, cardiovascular diseases, antiretroviral therapy

Introduction

The human immunodeficiency virus (HIV) is the causative agent of AIDS. There are 40 million people infected with HIV around the world. Mexico reported 178,310 people infected with HIV in 2019 (SS/CENSIDA, 2019). Research has suggested a relationship between plasma levels of Klotho protein and carotid atherosclerosis, where low levels of Klotho were correlated with carotid intima-media thickness (IMT) in HIV-infected subjects undergoing combined antiretroviral therapy (cART) (Jeong *et al.*, 2013). Klotho protein is expressed in the kidney, the parathyroid glands, the choroid plexus, in the Wnt signaling pathway, and others that govern aging, phosphate homeostasis regulation, and insulin metabolism (Mencke and Hillebrands, 2017). Low levels of Klotho are related to cardiovascular disease (CVD), atherosclerosis, and vascular calcification. Early investigation on the relationship between plasmatic Klotho and CVD was performed in 2011 by Semba *et al.*, (2011) where their analysis included common cardiovascular risk factors such as age, sex, total cholesterol, high-density lipoprotein (HDL) cholesterol, systolic blood pressure, and diabetes. Interestingly, CVD risk was lower in adults with high plasmatic Klotho levels. Corsetti *et al.* (2016) found that Klotho proteins were expressed in human cardiomyocytes, while expression of stress-related molecules increased significantly, suggesting that cardiac expression is downregulated in patients with higher cardiovascular risk.

Different studies suggest a relationship between low levels of Klotho and CVD in HIV-seropositive patients undergoing antiretroviral therapy. Several polymorphisms of the human *Klotho* gene have been associated with different cardiovascular events (Kuro-o, 2011). Klotho acts as a calcification inhibitor and mediates the response of vascular cells to FGF23 (Lim *et al.*, 2012). There are two Klotho protein isoforms, one is integrated into the membrane and the other one is secreted by the cell. The secreted Klotho is found in blood, cerebrospinal fluid, and urine of mammals. In the membrane, Klotho is a regulator for several transport mechanisms such as calcium channels, excitatory amino-acid transporters coupled with Na^+ (such as EAAT3 and EAAT4), co-phosphate transporters coupled with Na^+, NaPi-IIa, and NaPi-IIb, and Na^+/K^+ ATPase transporter (Sopjani *et al.*, 2014). Thus, our aim is to provide an overview of the role of Klotho on terms of its relationship

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with oxidative stress (OS) and metabolic disturbances in HIV-positive people on antiretroviral therapy. (Here, we changed the aim).

Methods

Literature review and article selection

We queried the PubMed NCBI, PLoS One, and MEDLINE databases for the time range corresponding to January 2000 to February 2019.Two conceptual references conducted during 1992 and 1997 were included as well. The query was performed through optimized strategies for each database to find articles related to HIV, cART, and OS, under the theoretical basis of CVD development in subjects with HIV-cART and its relationship with signaling pathways altered by OS. The selection criteria were Klotho-HIV, OS-HIV, ART-HIV, and Klotho-HIV-OS. We used English as the search language. Specific abbreviations, full words, and proximity operators were used for query thoroughness. In addition, the query was conducted with the assistance of the digital Library of the *Universidad Autónoma de Coahuila*, Torreón, Coahuila, Mexico. After discarding duplicate articles, the query resulted in 205 references.

Original and systematic review articles approaching the possible association among HIV, OS, and CVD were selected. Titles and abstracts were classified according to predefined inclusion and exclusion criteria. Inclusion criteria for Klotho reference consideration were dyslipidemias, atherosclerosis, systemic arterial hypertension, and coronary artery disease (CAD). Articles outside of refereed or indexed journals, address in kidney receptors, animal studies, *in vitro* experimental work, cancer, predictive biomarkers, bone diseases, and neurotoxicity were excluded. Inclusion criteria for OS, took into account articles related to metabolic alterations in HIV and cART. Articles related to OS and other diseases were excluded. After careful review and selection, 132 articles were removed. One hundred twenty-six of the total did not match the inclusion criteria and the other six were summaries. Finally, only 73 articles met the criteria to be included in this review.

Klotho structure and function

The Klotho protein is a hormone with antiaging activity that was identified in 1997 by Kuro-o *et al.* The *Klotho* gene is classified into α, β, and γ isoforms. In humans, α-*Klotho* is located in the long arm of chromosome 13. It is more than 50 kb long, contains 5 exons (Matsumura *et al.*, 1998), and encodes a membrane protein that has sequence similarity with beta-glucosidases. Klotho protein is composed of 1012 amino acids and it is found in the plasma membrane and Golgi apparatus (Kuro-o *et al.*, 1997), where it forms a complex with fibroblast growth factor receptor (FGFR) (Fon Tacer *et al.*, 2010).

α-Klotho is a coreceptor for the physiological signaling of FGF23, which is essential in the regulation of mineral metabolism, mainly in phosphate homeostasis. It maintains circulating phosphate within a narrow range by modulating intestinal phosphate absorption, urinary phosphate excretion, and bone phosphate distribution rather than in soft tissue; all in concerted interaction with other calcium-phosphotropic hormones such as PTH, FGF23, and 1,25-(OH)2 vitamin D. This protein is predominantly expressed in the kidney and brain (Kuro-o *et al.*, 1997).

The antiaging effects of α-Klotho has been also attributed to inhibition of the insulin-like growth factor signaling pathway, which is a mechanism conserved by evolution that suppresses aging sKl-mediated inhibition of insulin/IGF-1/PI3K signaling, which may act against aging by inducing resistance to OS. The insulin/IGF-1/PI3K pathway is linked to OS via FoxO forkhead transcription factors (FOXOs), which are downstream targets of the insulin-like signaling pathway regulating aging (Kenyon, 2005; Dalton *et al.*, 2017).

The β-*Klotho* gene was identified in 2000, based on sequence similarity to that of the α-*Klotho* gene (Ito *et al.*, 2000; Kuro-o, 2008). β-*Klotho* is located in chromosome 4, composed of 5 exons and 1044 amino acids; it is expressed in liver and adipose tissue. This protein increases the synthesis of bile acids by amplifying the expression of the *CYP7A1* gene, which encodes an enzyme affecting the synthesis of bile acids in the liver and forms a binary complex with FGFR1c, which in turn functions as a coreceptor of FGF21 (Inagaki *et al.*, 2005; Kuro-o, 2008; Kharitonenkov, 2009). Thus, β-Klotho is essential for the activity of FGF21 on different target tissues (Gallego-Escuredo *et al.*, 2012; Moure *et al.*, 2018). A β-Klotho-FGFR4 binary complex is required to bind to FGF19 to complete its biological activity. This at least partially explains why defects in FGF15, FGFR4, or β-Klotho result in identical phenotypic consequences such as an increase in liver bile acid synthesis (Kuro-o, 2008). Moreover, Klotho, as a complex component with FGF23, functions as an essential cofactor for activating FGF signaling (Kurosu *et al.*, 2006). The Klotho-FGFRs complex activates signaling cascades involving Erk1/2, SGK-1, and WNK4 for the reabsorption of Ca^{+2} mediated by TRPV5 (Andrukhova *et al.*, 2014). Therefore, in the cell membrane, Klotho works as a coreceptor of FGF23 to regulate phosphorus (Pi) and Ca^{+2} homeostasis. It is also considered an antiaging protein with a pleiotropic effect that protects organs (Kuro-o *et al.*, 1997). On the contrary, decreased levels of Klotho have been associated with high prevalence and rapid progression of CVD, atherosclerosis, and vascular calcification (Preedy and Watson, 2017).

γ-Klotho proteins are type I single-pass transmembrane proteins with sequence similarity to family 1 β-glycosidases, but lack dual conserved glutamic acid residues that are essential for enzymatic glycosidase activities; this protein is expressed in kidney and skin (Ito *et al.*, 2000, 2002; Dalton *et al.*, 2017). (short description gamma Klotho).

Genetic factors, Klotho *gene, and CVD*

While some variants of *Klotho* have been associated with longevity, others have been associated with atherosclerosis and cardiovascular event risk. In addition, more than 10 SNPs in this gene have been linked to kidney diseases, CAD, stroke, and loss of bone mineral density (Majumdar *et al.*, 2010). The functional *KL-VS* variant includes six SNPs in perfect linkage disequilibrium, two of which result in amino acid substitutions F352V and C370S that alter *in vitro* secretion, activity, and functionality of Klotho protein (Arking *et al.*, 2002, 2005; Donate-Correa *et al.*, 2016);

The single variant F352V, which is used to tag the KL-VS haplotype, is the result of replacing phenylalanine to valine at position 352. The functional variant KL-VS has a prevalence of 15.7% in the general population and has been linked to increased cardiovascular risk in Caucasians and African Americans, because carriers of this variant show high levels of serum cholesterol and high systolic blood pressure (Arking *et al.*, 2002, 2005; Majumdar *et al.*, 2010; Nzietchueng *et al.*, 2011; Donate-Correa *et al.*, 2016). Similar results have been seen with polymorphism G395A located at the promotor, being GG the wild-type genotype, while AG and AA are mutant. (What does GA+ AA mean? The explanation is needed. Here, we changed the meaning) (Hao *et al.*, 2016).

Relationship among Klotho, atherosclerosis, and HIV

Atherosclerosis is a progressive inflammatory disorder causing CAD and stroke, which are leading causes of worldwide mortality and morbidity (Lusis *et al.*, 2004). CVD associated with atherosclerosis, together with acute myocardial infarction (MI) and stroke, are the current leading causes of mortality among HIV+ patients (D'Ascenzo *et al.*, 2012, 2015; Smith *et al.*, 2014; Gili *et al.*, 2016; Kearns *et al.*, 2017; Vachiat *et al.*, 2017). High frequency of atherosclerotic CVD in HIV patients has been well documented, but underlying mechanisms for this condition have not been completely established. Three key sequential biological processes have been proposed as responsible for accelerating the atherosclerosis progression in HIV patients: (1) inflammation, (2) transformation of monocytes into macrophages and then into foam cells, and (3) foam cell apoptosis leading to development of atherosclerotic plaque through the Ca^{+2} pathway (Ca ++ should be written Ca 2+), regardless of endoplasmic reticulum stress (Shrestha *et al.*, 2014).

In 2013, Jeong *et al.* established a relationship between Klotho levels and carotid atherosclerosis in seropositive subjects. They showed that Klotho plasma levels were inversely associated with carotid intima-media thickness in HIV-infected subjects treated with cART. Thus, plasma levels of Klotho could be a useful biomarker for predicting atherosclerosis in HIV-infected patients (Jeong *et al.*, 2013).

In 2018, Moure *et al.* reported that HIV-infected patients had increased circulating levels of the antidiabetic hormone fibroblast growth factor 21 (FGF21) in their blood. By contrast, they stated that the expression of FGF21 was reduced in these target tissues (hepatocytes and adipocytes). Several antiretroviral drugs used in HIV therapy, belonging to different drug classes, have been identified as causing disturbances in the FGF21/KLB system in cultures of hepatic, adipose, and muscle human cells. These drugs caused reciprocal FGF21 induction/KLB/repression alterations that commonly occur in HIV patients undergoing antiretroviral treatment (Moure *et al.*, 2018).

OS in HIV patients

OS is defined as the increased production of reactive oxygen species (ROS) with a concomitant decrease in the antioxidant defense system (Repetto *et al.*, 1996; Schwarz, 1996; Therond *et al.*, 2000; Mollace, 2001; Sharma, 2014; Williams *et al.*, 2017). OS is involved in the pathogenesis of inflammatory diseases (Bhattacharyya *et al.*, 2014; Kelesidis *et al.*, 2016) and may impair antiviral immune responses (Price *et al.*, 2005; Kelesidis *et al.*, 2016). Infections involving a large group of etiological agents cause acute or chronic diseases and are main causes of morbidity and mortality. Infections can trigger the production of ROS and reactive nitrogen species; for example, infections caused by hepatitis viruses (B, C, and D), influenza A, Epstein–Barr virus, and HIV. These are the result of chronic persistent inflammation caused by virus replication and activation of macrophages and T cells (Inagaki *et al.*, 2005). OS increases the replication of HIV and several certain cytokines. TNF-α cytokine promotes OS directly by activating NF-κB and indirectly by activating different genes (Droge *et al.*, 1994; Okechukwu, 2015). OS may contribute to several aspects of HIV disease, including viral replication, inflammatory response, and decreased immune cell proliferation. For this reason, exogenous antioxidant supplements, such as natural compounds, and new-generation antioxidants neutralizing free radicals might represent an important additional strategy for HIV-infected patients undergoing cART treatment or highly active antiretroviral therapy (HAART) (Papadopulos-Eleopulos *et al.*, 1991; Sharma, 2014).

OS was observed for the first time in the pathology of AIDS a few years after the discovery of HIV, and it plays an important role in the progression of this condition (Sharma, 2014; Masiá *et al.*, 2016). In addition, there is evidence that OS due to HIV contributes to neurodegenerative complications observed in patients with AIDS (Ivanov *et al.*, 2017) and causes a reduction in cellular antioxidant defenses (Schieber and Chandel, 2014; Jacob Victorino *et al.*, 2015; Nsonwu-Anyanwu *et al.*, 2017). In HIV-infected patients, glutathione (GSH) is depleted in plasma, lymphocytes, monocytes, and pulmonary epithelial mucosa (Hans-Peter *et al.*, 1989; Staal *et al.*, 1990; Couret and Chang, 2016). Depletion of GSH is inversely correlated to glutathione disulfide (GSSG) increase, compromising defense against free radicals (Couret and Chang, 2016). As ROS are oxygen intermediates with a high capacity to react against various biological molecules (Augusto and Miyamoto, 2011; Gutowski and Kowalczyk, 2013), they are responsible for direct damage of cellular structures within the vascular wall and for triggering a number of redox-sensitive transcriptional pathways (Margaritis, 2019).

ROS production is carried out in various cellular processes such as electron leakage from mitochondrial transport chain, lipid, amino acid, and biogenic polyamine degradation, and protein folding endoplasmic reticulum's lumen. Superoxide anions are generated in the mitochondria. HIV infection causes OS, because monocytes of infected individuals have a higher production of ROS (Elbim *et al.*, 1999). Intracellular GSH plays an important role in the regulation of transcription and replication of the HIV (Staal *et al.*, 1992). So, compensation for pathogenic effects of HIV-1 replication requires intact ROS detoxifying enzyme function. However, HIV-infected individuals show a reduction in total antioxidant capacity (Teto *et al.*, 2013; Nsonwu-Anyanwu *et al.*, 2017), which was detected in T lymphocyte subsets, $CD4^+$, and $CD8^+$ cells. Intracellular GSH levels regulate the T lymphocyte function (Staal *et al.*, 1990), and antiretroviral therapy restores $CD4^+$ cell and T lymphocytes levels; yet, it increases the imbalance of the redox state (Elias *et al.*, 2013) (Fig. 1).

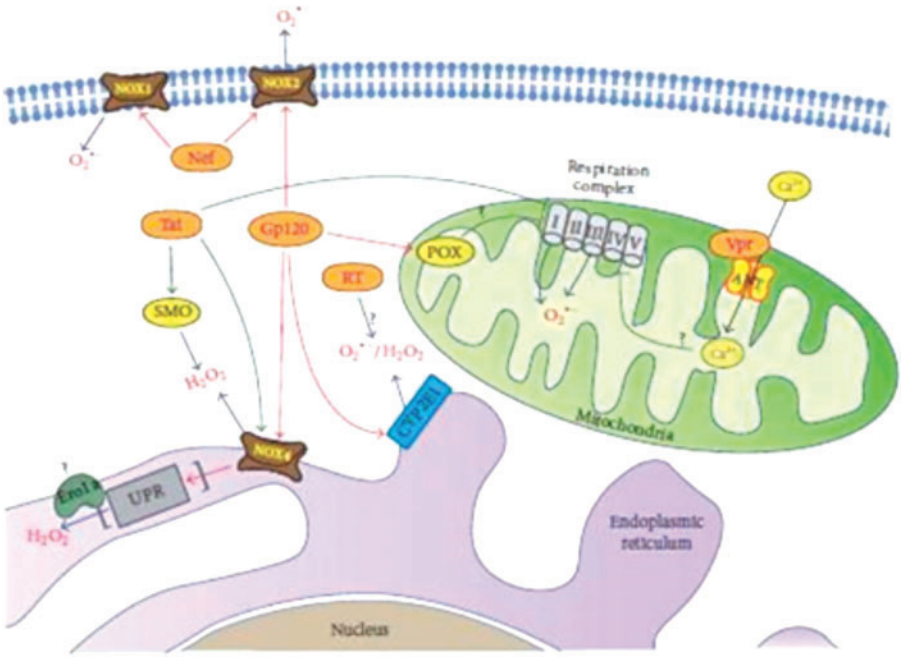

FIG. 1. Cellular sources of ROS in HIV infection. Several HIV proteins improve ROS production. Viral proteins include, among others, the envelope protein Gp120, Tat, Nef, Vpr, and RT. The envelope protein Gp120 improves the production of ROS by the positive regulation of cytochrome P450 2E1 (CYP2E1), proline oxidase (POX), and the activation of NOX2 and NOX4. Tat induces spermine oxidase (SMO), an enzyme involved in the catabolism of biogenic polyamines, and can affect the function of mitochondria. Tat also activates NADPH (but not xanthine) oxidases and in particular NOX4, which in turn can induce another peroxide-generating enzymes involved in the unfolding protein response (UPR) such as oxide-reducing ER 1α (Ero1α). Vpr protein interacts with the adenine nucleotide translocator (ANT), a component of the mitochondrial permeability transition pore (PTP) involved in $Ca+^{2}$ influx in mitochondria. The Nef protein can directly interact with the p22phox subunit of NADPH oxidases without affecting NOX expression. Finally, RT triggers ROS production by mechanisms not yet discovered. HIV, human immunodeficiency virus; ROS, reactive oxygen species. Color images are available online.

OS in antiretroviral therapy (HAART)

HAART may increase circulating reactive chemical species due to production of more oxidized metabolites derived from interaction between ROS and biomolecules from infected cells (Margaritis, 2019). Antiretroviral drugs for HIV therapy are used in combination with regimens for preventing viral replication. However, these therapies are associated with significant side effects such as diabetes, hypertension, atherosclerosis, and cardiovascular complications, due to an increase in OS. OS can interrupt endothelial homeostasis by causing an imbalance between antiatherogenic factors such as HDL (Hulgan *et al.*, 2003a).

Changes in lipid metabolism during HIV-1 infection are a consequence of the critical role of cholesterol on HIV-1 replication, thus affecting levels of HDL cholesterol, low-density lipoprotein (LDL) cholesterol, very LDL, and triglycerides, as well as lipid peroxidation, one of several factors related to atherosclerosis development in HIV-1 patients (Elbim *et al.*, 1999). In addition, changes in lipid metabolism are also related to toxicological effects such as hepatotoxicity, cardiotoxicity, hematotoxicity, and nephrotoxicity. The relationship between OS, cART, and mitochondrial dysfunction has been documented, and it is related to mitochondrial DNA inhibition by alternations in the Krebs cycle and increased levels of ROS (Sundaram *et al.*, 2008; Masiá *et al.*, 2016). This suggests that HIV-1 infection, alone or in combination with cART, may induce OS, increasing the pathogenic effect (Hulgan *et al.*, 2003b; Sharma *et al.*, 2014). Further studies are necessary to establish the molecular correlation between toxicity of antiretroviral therapy and OS (Fig. 2) (Reyskens and Essop, 2014).

OS and its relationship with Klotho

Klotho protein is a hormone that inhibits insulin and insulin-like growth factor 1 (IGF-1) signaling; and it increases resistance to OS. Klotho binds to the FGFR receptor, activating AKT (Ogawa *et al.*, 2007) and FoxO1 transcription factors (forkhead1), which are negatively regulated by the insulin/IGF-1 signaling pathway, inducing the expression of manganese superoxide dismutase, facilitating the elimination of ROS, thus providing resistance to OS (Fig. 3). (Yamamoto *et al.*, 2005; Richter *et al.*, 2016). Research has suggested that Klotho may function as an important humoral factor involved in oxidative decrease in serum. Klotho has also been reported as a predictor of atherosclerosis (Keles *et al.*, 2015) stress regulation, endothelial dysfunction, cell proliferation, and apoptosis (Kokkinaki *et al.*, 2013), because it has been seen that increased levels of soluble Klotho are correlated to a reduction in cardiovascular risk (Navarro-González *et al.*, 2014).

There is limited information regarding Klotho protein decrease in HIV-positive people on cART, and how it can

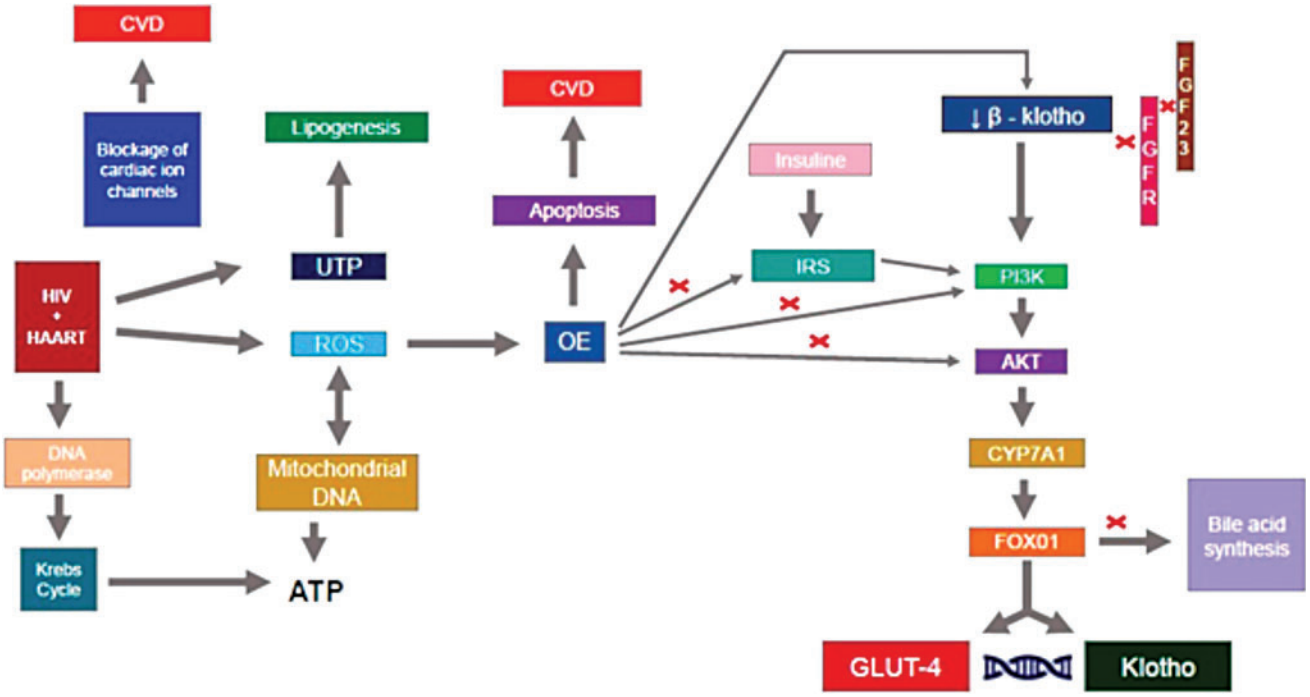

FIG. 2. Hypothetical model of the relationship between HIV-cART-β-Klotho and FGF23, in the development of the CVD. AKT, protein kinase B; cART, combined antiretroviral therapy; CVD, cardiovascular disease; CYP7A1, cytochrome P-450 7 A1; FGFR, receptor for fibroblast growth factor; FOXO1, forkhead box protein O1; GLUT4, type 4 glucose transporter; IRS, insulin receptor; PI3K, phosphatidylinositol 3 kinase; OS, oxidative stress; SUP, ubiquitin or protease system (Based on the model of Reyskens and Essop, 2014). Color images are available online.

influence the development of CVDs. So, several studies suggest that cardio protective activity would be affected by HIV infection or by exposure to treatment due to the decreasing of Klotho protein (here, we try to explain why it is necessary to investigate about Klotho). With the introduction of ART, the life span of HIV-positive subjects has increased dramatically. The aging of these subjects make them vulnerable to various diseases, including CVDs. Further, HIV induces OS, which in turn increases HIV replication. This can lead to an increased risk of CVDs. Klotho protein is reported to have antiaging activity.

The increased risk of CVDs in HIV could be due to the abovementioned factors. If this is so, to what extent the Klotho protein could contribute to developing CVDs in HIV

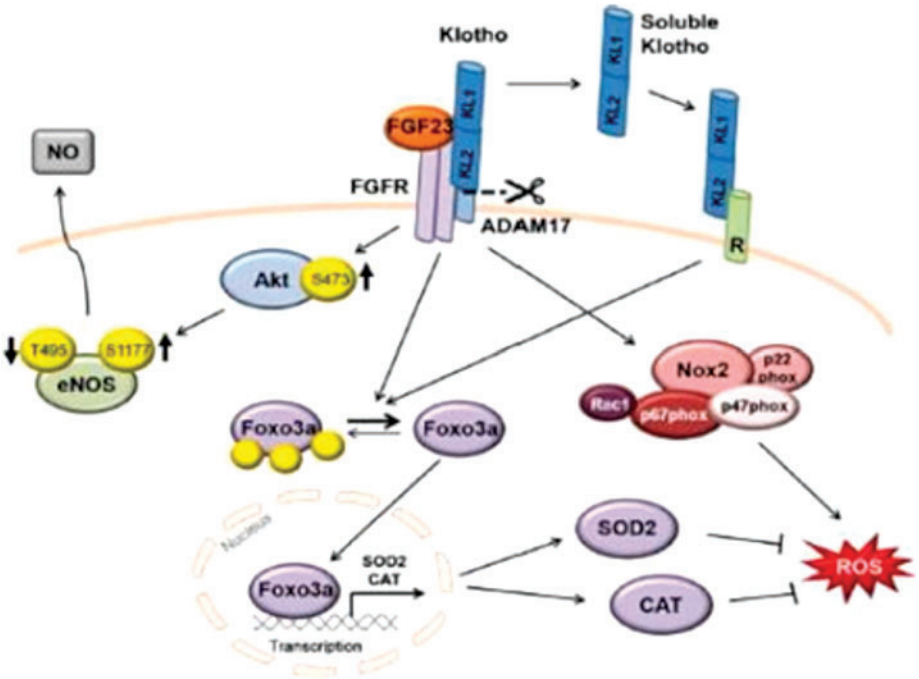

FIG. 3. Relationship between Klotho and OS. Under physiological conditions, the binding of FGF23 to the FGFR/Klotho complex induces nonmediated release by activation of Akt and eNOS, and stimulates the formation of ROS via p67phox-, p47phox-, Rac1, and p22phox mediated by Nox2 activation. In addition, FGF23 protects against OS through FGFR/Klotho-modified, a mediation of Foxo3 in the expression of SOD2 and CAT. In addition, FGF23 and the expression of the ADAM17 protease, and subsequently, the release of soluble Klotho. The binding of soluble Klotho to a still unknown receptor (R) promotes the degradation of ROS through SOD2 induced by Foxo3a and the expression of CAT. Color images are available online.

subjects after accounting for OS, increased life span with the use of ART (aging), and premature aging induced by HIV?

Conclusion

In conclusion, we have observed that HIV infection, OS, and oxidation of the Klotho receptor decrease insulin receptor signaling, affecting GLUT4 transcription, MAPK, FOX01, cell differentiation, adipogenesis, and other signaling pathways, which can affect various organs, including the heart. Exposure to HAART increases ROS, causing metabolic alterations and low Klotho expression, thus increasing cardiovascular risk and the onset of diseases such as atherosclerosis or MI. More studies are needed to understand the mechanisms related to Klotho receptors and their complications in relationship to obesity, inflammation, and metabolism in people with HIV-AIDS exposed to HAART to improve the therapies and patient quality of life.

Disclosure Statement

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