Novel Role of Transcriptional Factor Kaiso in HIV Infection

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Abstract: The role of Kaiso, a POZ-ZF transcriptional factor in HIV infection, which has been disparagingly affecting African Natives as well as African Americans, has not been well studied. For these reasons, this research aimed to investigate the level of expression and the role of Kaiso in HIV-1 infected African Natives compared with patients in the United States. *In silico* data of 185 whole blood samples were analyzed to study gene expression by array in GEO (Gene expression Omnibus) dataset from the National Center for Biotechnology Information (NCBI). Different bioinformatics approaches were used to analyze the data. Two or more groups of samples were compared using GEO2R to identify differentially expressed genes across experimental conditions. Pathways that were significantly associated with specific gene sets were determined by Gene Set Enrichment analysis (GSEA). Results showed higher level of Kaiso expression in HIV-1 patients compared to healthy control (p = 3.89e-10), and it was significantly higher in African Natives compared to United States patients (p = 0.002). Importantly, this study revealed a negative correlation between Kaiso expression and CD4+ T cell count in HIV-1 infected African Native patients (p = 0.003). This negative correlation between Kaiso and CD4+ T cell count was accompanied by increased viral load in African Natives with a higher viral set point compared to US HIV-1 patients. These data may at least partly explain the reasons for faster progression to AIDS in African Natives than seen in US patients. Kaiso associated enrichment pathways showed that Kaiso upregulation may contribute to CD4 depletion in HIV-1 infection, and may upregulate HIV associated neurological impairment marker genes. The results also showed that Kaiso expression may also be associated with increased Wnt/β-catenin signaling pathway by downregulating GSK3β, MAPK1 and MAPK3 through different downregulated pathways in African Native patients. This study suggests that Kaiso may play a role in the crosstalk between different pathways in HIV-1 infection. In conclusion, the present study suggests, for the first time, that Kaiso expression levels may possibly play a role in the faster acceleration of HIV-1 infection towards AIDS in African ancestry patients and this may be through the involvement of Wnt/βcatenin signaling pathway. Data of this study also suggests that Kaiso expression level may contribute to increased crosstalk between different pathways in HIV-1 pathogenesis. Further studies are needed to fully delineate the role of Kaiso in different HIV1 infected ethnic groups through the involvement of different intermediary pathways.

1 INTRODUCTION

Since the first reports of AIDS cases in early 1980s, \HIV virus around the world and approximately 32 million people have died. The African region remains most severely affected, with nearly one in every 25 adults (4.1%) living with HIV and accounting for nearly two-third of the people living with HIV worldwide (WHO, https://www.who.int/gho/hiv/en/). More than half (54%) of the people living with HIV infections around the world are from East and South Africa (UNAIDS'AIDSinfo', 2019).

However, different studies reveal that infection with HIV occur more in African born black immigrants rather than U.S. born blacks (Johnson et al., 2010; Kent, 2005; Kerani et al., 2008; Ashton et al., 2012) and HIV prevalence was higher in African born compared to US born blacks and US white (Ashton et al., 2012). Racial disparities have been indicated in both HIV-1 (CDC, 2017; Hall et al., 2007; Klein et al., 2014) and in different human cancers (Abisoye-Ogunniyan et al., 2018; Bassey-Archibong et al., 2017; Jones et al., 2014; Jones et al., 2012; Jones et al., 2015; Wang et al., 2016).

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Kaiso is Caribbean slang for calypso music, which accompanied the late-night cloning of this gene. Kaiso is a 672 amino acid protein belonging to the BTB/POZ (broad complex, tram track, bric à brac/pox virus and zinc finger) family of zinc finger transcription factors (Albagli et al., 1995; Bardwell and Treisman, 1994). In contrast to many transcription factors, Kaiso as a transcriptional regulator with bimodal DNA-binding specificity, which binds to methylated CGCG and to the non-methylated consensus KAISO-binding site (KBS) TCCTGCNA. A few reports have been published illustrating the role of Kaiso in different types of cancers (Pierre et al., 2019). In addition, Kaiso expression is correlated to racial disparities in different types of cancer; some of these studies correlate the nuclear expression of Kaiso with aggressiveness of tumors and metastases in African Americans (US African) compared to white patients (Jones et al., 2014; Jones et al., 2012; Bassey-Archibong et al., 2017).

To our knowledge, no studies have been reported so far on the expression levels of Kaiso in HIV-infected people of different ethnic backgrounds/ races and the role Kaiso may play in infection and replication of HIV. For these reasons, the objective of this study were to investigate the role of Kaiso expression by analyzing *in vivo* HIV-1 infected patients dataset (NCBI) in different races and ethnic groups. Bioinformatics and statistical analysis tools are used to analyze data.

2 MATERIALS AND METHODS

To achieve our aim to determine the expression levels of Kaiso in HIV-infected and uninfected people of different ethnic/racial backgrounds, *in silico* data of 185 whole blood samples (from United States, and Africa) with or without HIV-1 infection was analyzed by gene array to study gene expression. Geo dataset from the NCBI's (National Center for Biotechnology Information) Gene expression Omnibus (GEO) accessible through GEO Series accession numbers GSE29429 were used GSE# (http://www.ncbi.nlm.nih.gov/gov/query/acc.cgi?acc=GSE#).

The gene symbol names associated with each data set were pulled from each GPL file and merged with its GSE read using the R merge function. Gene expression data were analyzed to determine the role of Kaiso in HIV-1 infection.

2.1 Geo Dataset Analysis

To determine if Kaiso has a role in HIV-1 infection, expressed genes were subjected to data analysis using:

1. GEO2R, NCBI (ncbi.nlm.nih.gov/geo/geo2r/). GEO2R was used to compare two or more groups of samples in order to identify genes that are differentially expressed across experimental conditions, based on the R programming language that provides tools for the analysis of high-throughput genomic data. Results are presented as a table of genes ordered by significance. 2. GSEA (Gene Set Enrichment Analysis) http://software.broadinstitute.org/gsea/index.jsp. (http://software.broadinstitute.org/gsea/index.jsp) . GSEA is a computational method that determines whether a priorily defined set of genes shows statistically significant, concordant differences between two biological states (e.g., phenotypes). 3. RStudio (http://Rstudio.org) used for statistical computing and graphics. 4. Excel and XLSTAT for further analysis and graphics. 5. GraphPad prism for data analysis and graphics.

2.2 Statistical Analysis

Data are expressed as means ± standard deviation (SD). The significance of differences between healthy control and HIV-1 infected groups was evaluated using One Way ANOVA, Two Way ANOVA, and t-test analysis. Differences were considered significant when $P < 0.05$.

3 RESULTS

3.1 HIV-1 Demographic Data Analysis

Microarray gene expression profiles for 185 patients from Gene expression Omnibus (GEO) dataset were downloaded from the National Center for Biotechnology Information (NCBI). One hundred forty-seven samples were from HIV1 –infected patients and thirty-eight samples were from healthy control people (Table 1). Among the HIV-1 positive patients, 130 were male and 17 were females. Among the control healthy people, 22 were male and 16 were females (Table 1).

In this study, age range was 20-66 years old of whites and African American HIV-1 patients with the peak rate at the age of 38 and 28 respectively. While, age range was 18-38 for African Natives with peak rate at the age of 18 with infected patients.

Table 1: Clinical and pathological characteristics of HIV-1 patients-Whole Blood GSE29429.

Characteristic		Number of patients N=185				% of infected
Ethnicity	Total N=185	Healthy N=38	HIV N=147	ART –ve	ART +ve	
USA	91	11	80	20	60	87.9
Age group		21-47(31.1 ± 9.3)	20-66 (38.8 ± 13.6)			
African Native (AN)	94	27	67	67	0	71.3
Age group		19-48(28.8 ± 7.3)	18-38 (24.7 ± 5.2)			
Race/Gender						
White	68	7	61	14	47	
Male	63	2	61	14	47	100
Female	5	5	0	0	0	
Age group		22-47 (32 ± 9)	24-56 (39.4 ± 11.6)			
African American	23	4	19	6	13	
Male	18	4	14	5	9	73.7
Female	5	0	5	1	4	26.3
Age group		21-46 (29.75 ± 11)	20-66 (36.9 ±18.9)			
African Native	94	27	67	67	0	
Male	71	16	55	55	0	82
Female	23	11	12	12	0	18
Age group		19-48 (28.8 ± 7.3)	18-38 (24.7 ± 5.2)			

3.2 Kaiso Expression in HIV-1 Infection Is Significantly Associated with Gender, Race, and Ethnicity

Dataset were examined using R program for Kaiso expression, which was found to be upregulated in HIV-1 infected patients compared to healthy controls samples (Figure 1-A).

Of the 185 whole blood samples collected from acute HIV-1 patients (GSE29429), 94 samples were from African Natives and 91 samples were from the United States. Their clinical and pathological characteristics are shown in Table 1. Importantly, significant differences in Kaiso expression were observed among different race groups. Kaiso expression was significantly higher in African Natives as compared to both African Americans (US African) and White Caucasians (p = 0.004 and 0.04, respectively) (Figure 1-B). All the results after this step were analyzed by comparing African Natives to United States (U.S) patients since Kaiso were significantly higher in African Natives compared to U.S patients (p *value* 0.002) (Figure 1-C).

Results of RStudio analysis of Kaiso expression in HIV-1 infected and healthy control samples demonstrated higher Kaiso expression in HIV-1 patients compared to healthy controls. However, differences in the expression levels were not statistically significant (Figure 1-A). while, a highly significant difference was observed in males compared to females in acute HIV infected patients (p =0.002) (Figure 1-D).

Kaiso expression was significantly higher in both male and female African Natives compared to U.S acute HIV patients (p = 0.04) (Figure 1-E). Kaiso expression was also significantly higher in younger age African patients (mean age 24.7 ± 5.2) in comparison to U.S patients (mean age 38.8 ± 13.6) (p < 0.0001).

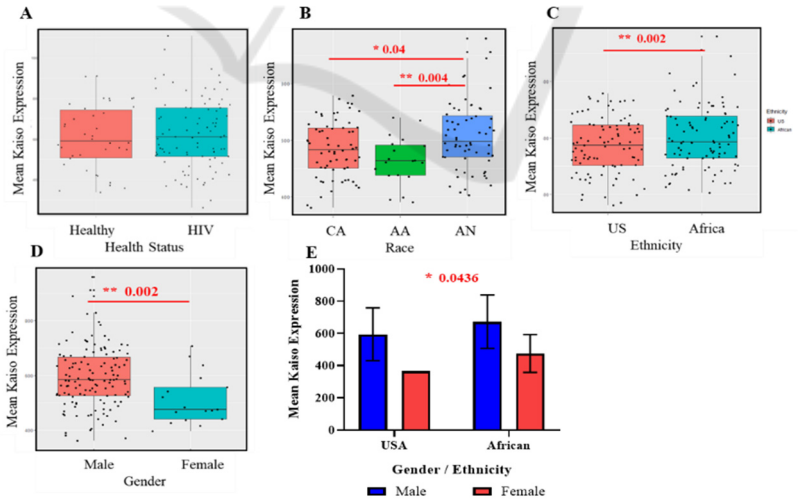


Figure 1: In HIV-1 infection, Ethnicity, Gender are significantly associated with High expression of Kaiso. R program used for the analysis and graphics A. Higher Kaiso expression in overall HIV patients (n=87) compared to healthy (n=38). B. Kaiso is significantly higher in African Native compared to African American (US African) and white Caucasian groups with p value 0.004 and 0.04 respectively. C. Kaiso is significantly higher in African ethnic group (n=67) in comparison to US patients (n=20) (p = 0.002). D. Significant gender differences (p = 0.002) in overall HIV males with high Kaiso expression compared to females, graphpad prism was used for significance analysis and the graphics that show a significant higher Kaiso expression in African ethnic HIV males and females compared to US males and females with p = 0.0436 (ANOVA test) as shown in (E).

3.3 Trends in Kaiso Expression during HIV Disease Course

Kaiso expression measured by weeks through HIV progression (from enrollment to week 24) in US and African patients, the results showed a significant higher rate of Kaiso expression in African patients compared to US HIV patients ($p = 0.0044$) (Figure 2-A).

However, a highly significant difference ($p = 0.0005$) in CD4+ T cells count was observed which was higher in U.S HIV patients through HIV progression measured by weeks compared to that of African Natives (Figure 2-B). Negative correlation was found between CD4 count and Kaiso expression in both U.S and African Natives patients Figures (2C and 2-D) respectively, with significant difference ($p < 0.0001$). in African Natives Patients.

HIV viral load measures the number of HIV particles or copies in a milliliter (ml) of blood cells. Viral load decreased overtime (Figure 2-E) in both African Natives and US patients. However, the viral load remained significantly higher ($p = 0.0417$) in African Natives (Figure 2-E).

3.4 Pathway Enrichment Analysis of Kaiso Associated Differential Expressed Genes

GEO2R from NCBI were used for each dataset to compare two or more groups of samples in order to identify genes that are differentially expressed through experimental conditions. The results presented as a table of genes ordered by significance. Significant genes (p *value* ≤ 0.05) were further analyzed using GSEA (gene set enrichment analysis), Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis were achieved for the differentially expressed genes.

In GEO2R, a comparison of HIV-1 infection to healthy control patients in both United States and African Native patients, heat maps used in order to identify genes expressed through high and low expression of Kaiso in both infected groups (Figure 3). Based on the analysis, a total of 530 differentially expressed genes were identified in US HIV-1 patients compared to healthy individuals, including 359 upregulated genes and 171 downregulated genes with $p < 0.05$ and fold change (FC) ≥ 1.5 set as the threshold criteria. However, 349 differentially expressed genes in HIV-1 infected African Native compared to healthy control individuals with 289 upregulated genes and 60 downregulated genes with $p < 0.05$ and FC ≥ 1.5.

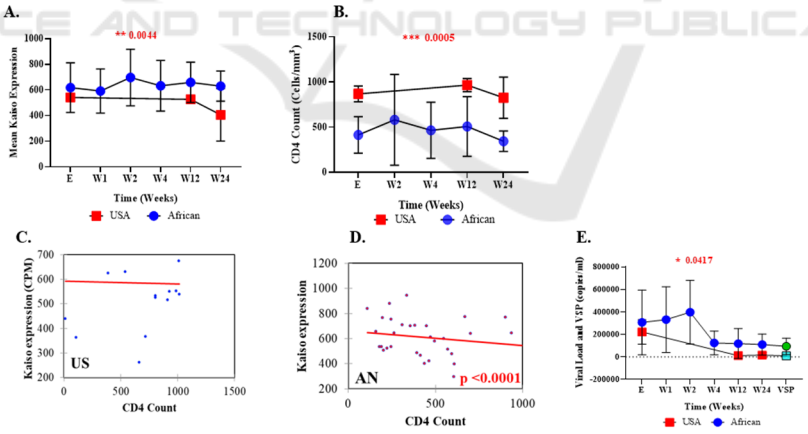


Figure 2: Negative significant correlation between Kaiso expression and CD4+ T cell count. A. Kaiso expression is significantly higher in African Natives patients during the progression of HIV-1 infection measured by weeks with a p value 0.004 compared to US patients. B. CD4+ T cells count increase in the first weeks of infection, but decline at week 24 in both study groups, however, CD4 count is lower in African Natives with highly significant difference ($p = 0.0005$) to US patients. C. & D. Negative correlation between Kaiso expression and CD4+ T cells count in both study groups but with a significant difference in African Natives (AN) ($p < 0.0001$). E. Viral load (VL) increase significantly and sharply at the first weeks of infection in African Natives patients compared to US patients ($p = 0.041$), VL drops rapidly to steady state of viral set point (VSP) the indicator of AIDS disease progression which is higher in African, this may indicate their progression to AIDS faster than US patients.

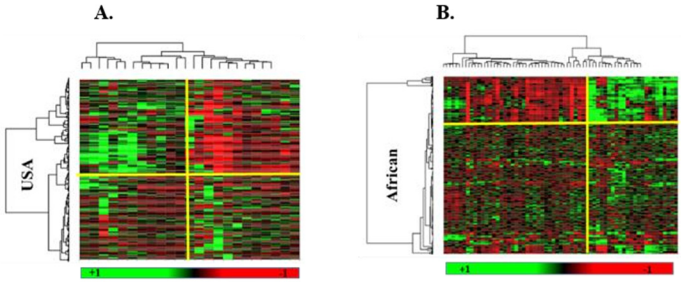


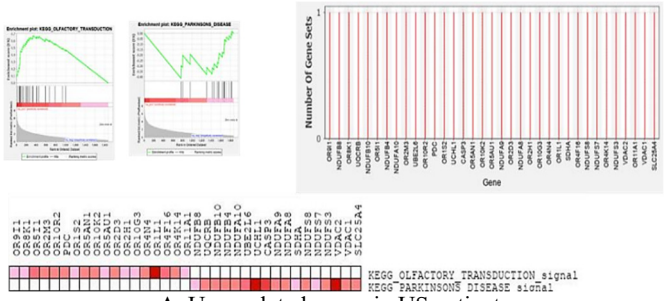
Figure 3: Gene expression analysis. Heat maps illustrating genes associates with Kaiso expression associated genes in: A. US HIV1 patients with 530 differentially expressed genes identified, including 359 upregulated genes and 171 downregulated genes with p <0.05 and fold change (FC) ≥1.5 set as the threshold criteria. B. African HIV-1 patients with 349 significant expressed genes, 289 upregulated genes and 60 downregulated genes with p < 0.05 and FC ≥1.5. Green color indicates upregulated genes in correlation to high Kaiso expression while red color indicates downregulated genes in correlation to high Kaiso expression. Columns indicated patients while rows indicated genes.

Finally, the differentially expressed genes were further analyzed by GSEA analysis for enriched KEGG pathways. The results showed two pathways correlated to Kaiso associated upregulated genes in US patients (Figure 4-A), including "olfactory transduction" and "Parkinson disease", while the Kaiso associated downregulated differentially expressed genes were enriched in eight pathways, "lysosome", "ribosome", "olfactory transduction", "cytokinecytokine receptor interaction", "JAK STAT signaling", "hematopoietic cell lineage", "dilated cardiomyopathy", "neuroactive ligand receptor interaction" (Figure 4-B). However, ten different pathways found in African high Kaiso differentiated associated upregulated genes which are, "cell cycle", "cytokine cytokine receptor interaction", "cell adhesion molecules CAMS", "P53 signaling pathway", "olfactory transduction", "progesterone mediated oocyte maturation", and "RNA degradation", "oocyte meiosis", "neuroactive ligand receptor interaction", "calcium signaling" (Figure 4C). Whereas, the Kaiso associated downregulated, differentially expressed genes were enriched in three pathways, "ribosome", "Al-Zheimers disease", "neurotrophin signaling" (Figure 4-D).

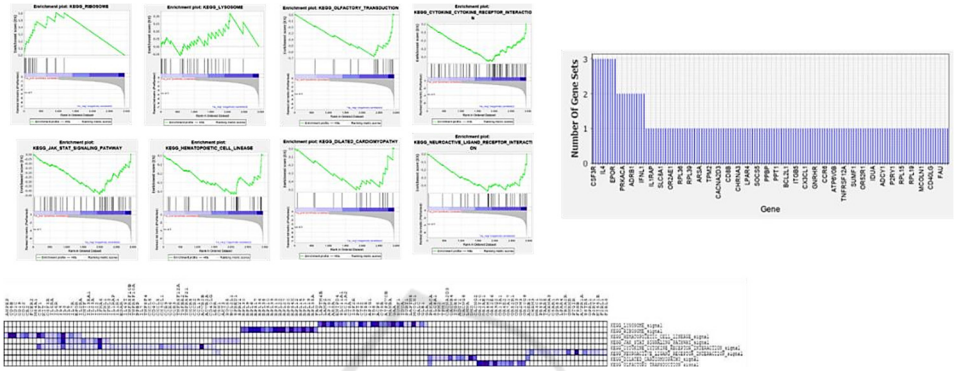
4 DISCUSSION

Racial/ethnic disparities related to HIV-1 infection and increased incidence of HIV-1 infection in African ancestry were described in 2016 in the CDC's HIV surveillance report (CDC 2017). HIV infections have been reported more in African born black immigrants rather than U.S. born blacks (Johnson et al., 2010; Kent, 2005; Kerani et al., 2008; Ashton et al., 2012) with higher prevalence in African born compared to Kaiso expression to HIV-1 pathogenesis. Results of US born blacks and US white (Ashton et al., 2012). Further, it is known that disease progression to AIDS is much faster in African Natives. However, the mechanisms underlying in these disparities and faster progression to AIDS in Africans has not been fully delineated. Several reported studies including published reports (Abisoye-Ogunniyan et al., 2018; Ahmed et al., 2019; Jones et al., 2014; Jones et al., 2012; Jones et al., 2015; Pierre et al., 2019) showed higher expression of Kaiso in patients with different cancers including prostate cancer. The level of Kaiso expression and the pathways linked to higher level of expression appear to be linked with a few intermediary pathways, including the Wnt pathway (Iioka et al., 2009). While some of these pathways have also been linked to the pathogenesis of HIV infections and the expression of several other immune-related genes, to our knowledge no studies have been reported showing the role of Kaiso in the pathogenesis of HIV infections. More importantly, level of Kaiso expression in HIV-infected African versus all HIV infected patients in the U.S. has not been reported.

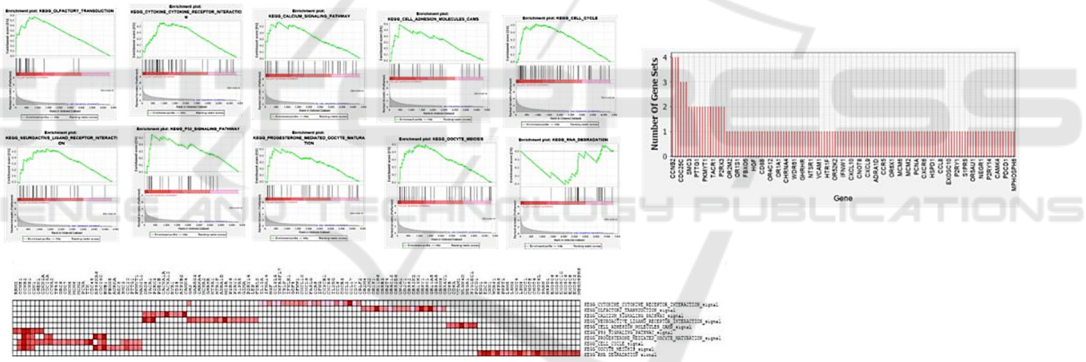
A significant finding in this data analysis is the higher level of Kaiso expression in HIV infected African patients compared to patients in the United States. This is the first study showing a significant negative correlation between Kaiso expression and CD4 count in HIV-1 infection (Figure 4). In addition, the viral load and viral set point (VSP) were significantly higher in African HIV-1 patients compared to US patients (p = 0.0417). A few other studies have referred to the importance of viral set point as a key indicator for HIV progression to AIDS and survival (Mellors et al., 1996; Quinn et al., 2000; Mellors et al., 1997). Clearly, no studies have been reported previously that correlated higher level of Kaiso expression to HIV-1 pathogenesis. Results of



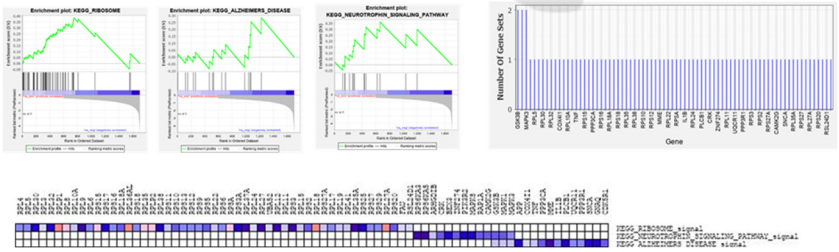
A. Upregulated genes in US patients



B. Downregulated genes in US patients



C.Upregulated genes in African Natives



D. Downregulated genes in African Natives

Figure 4: Pathways correlated to high expression of Kaiso. Enrichment plot, heat map, and leading-edge analysis for the gene sets of Kaiso associated differentially expressed genes identified in comparison between HIV infected US patients and African Native patients. A. US Kaiso related upregulated pathways genes. B. Downregulated pathways genes. C. African Kaiso related upregulated pathways genes. D. Downregulated pathways genes. Enrichment plot of the ranked list of significant genes ($p \leq 0.05$), and the heat map that shows the genes in the leading-edge subsets. In a heat map, expression values are represented by colors, where the colors (red, pink, light blue, dark blue) represent the range of expression values (high, moderate, low, and lowest) where red colored are upregulated genes and dark blue are downregulated genes. Bar graphs shows each gene and the number of subsets in which it appears.

this data analysis study gives a preliminary indication that higher rate of HIV progression to AIDS in African patients compared to US patients may at least partly be due to higher level of Kaiso expression.

The host factor β-catenin is the main component of Wnt/β- catenin-signaling pathway. A study by Iioka et al, 2009 found that, Kaiso functions as a bimodal regulator of canonical Wnt signaling as Kaiso enhanced Wnt/β-catenin signaling when it has mild ectopic expression. While, moderate and higher expression of Kaiso inhibited Wnt/βcatenin signaling and Kaiso knockdown appears to suppress Wnt/β-catenin activity. The same study showed that Kaiso

Binding to HDAC1 may inhibit the complex formation between β- catenin and HDAC1 and this may increase the negative effects of HDAC1 from the β- catenin/TCF complex (Iioka et al., 2009). Nonetheless, Wnt/β- catenin signaling has been shown to interact with the life cycle of HIV-1during infection and latency (Al-Harthi, 2012).

Different studies found that Wnt/β-catenin pathway may be involved in HIV pathogenesis as TCF4 has been shown to represses Tat-mediated transactivation of HIV promoter (LTR) in astrocyte cells (Wortman et al., 2002; Rossi et al., 2006; Carroll-Anzinger et al., 2007). Wnt β-catenin signaling interacts with the life cycle and replication of human immunodeficiency virus type-1 in different target cells including, peripheral blood mononuclear cells and astrocytes (Al-Harthi, 2012).

Our study revealed that upregulation of Kaiso is associated with upregulation of olfactory function genes in both US and African patients (Figure 4-A and C), which act as a marker of HIV associated neurological impairment (Serby et al., 1992). Studies have shown that HIV infected patients with neurocognitive impairment had diminished odor sensitivity (Brody et al., 1990; Hornung et al., 1998; Razani et al., 1996). In addition, high expression of Kaiso was detected as methyl CpG binding protein in nervous system cells (NS) (Martin Caballero et al., 2009). In comparison, Kaiso improves the locomotion mechanism and depressed behavior in a review of Kaiso protein as a brain and behavior regulator, Kaiso deficient mice has shown antidepressant-like effect (Kulikova and Kulikov, 2018). Yet, Parkinson disease may develop early in HIV infection following viral infection within the basal ganglia or late in the disease course in combination with AIDS dementia complex (ADC), or as a result of underlying chronic neuroinflammation leading to basal ganglia dysfunction, altered blood-brain barrier (BBB) permeability, and neurodegeneration (Berger et al., 2000).

Our study also revealed that Kaiso associated pathways of African upregulated genes are p53, cell cycle and CAMS (Figure 4-C). Cell cycle dysregulated after HIV infection due to the virus dominating cellular transcriptional machinery to increase viral replication and proliferation (Devadas *et al*., 2016). While, p53 is the main factor in host restriction of HIV-1 replication and infection (Mukerjee et al., 2010). However, the infection with the virus enhances the expression of p53 in primary CD4+ T cells (Imbeault et al., 2009a; Imbeault et al., 2009b) in addition, p53 facilitates HIV-1 binding to host cells by increasing expression of CD4 and integration into host chromosome through upregulation of integration cofactor p75 (Wang et al., 2017a) and the activation of p53 target genes will lead to cell apoptosis (Genini et al., 2001). Kaiso may contribute to CD4 depletion in HIV-1 infection since Kaiso regulate p53 and increase cell cycle arrest and apoptosis (Koh et al., 2014) Yet, apoptosis could be inhibited by blocking the interaction between Kaiso and p53 by NF-kB (RelA/p65) expression which also lead to depletion of nuclear Kaiso and sequestering Kaiso in the cytoplasm (Koh et al., 2015). NF-kB (RelA/p65) is important for HIV-1 transcription initiation in primary infection and in reactivation of HIV-1 latently infected cells (Wang et al., 2017b).

One of the upregulated pathways in African HIV-1 infected patients correlated to high expression of Kaiso is cell adhesion molecules (CAMs) that play a basic role in regulating immune cell function such as immune cell trafficking into tissues, cell proliferation and immunological synapse formation during homeostasis, inflammation and cancer (Harjunpää et al., 2019). Circulating cell adhesion molecules such as intracellular adhesion molecule-1 (ICAM-1) and vascular adhesion molecule-1 (VCAM-1) are significantly increase in HIV positive and AIDS patients (Greenwood et al., 1998; Seigneur et al., 1997). Also, HIV-1 gp120 significantly upregulate ICAM-1 on brain endothelial cells in animal model (Toneatto et al., 1999)) and increase ICAM-1 in glial cells and leukocytes (Ren et al., 2002).

Cell adhesion cofactor p120-catenin, is the only known binding partner for Kaiso (Daniel and Reynolds, 1999). Interestingly, in another study by Rodova et al, (2004) revealed that catenin delta which is a brain-specific member of the p120 catenin subfamily, create a complex with Kaiso and this complex may regulates synapse-specific transcription at the neuromuscular junction (Rodova et al., 2004). Although multiple studies documented the role of Kaiso in different cancer types, there are no studies determining the Kaiso role in HIV-1 infection. In

summary, this study with bioinformatics analysis of the HIV infected patient data showed that Kaiso expression is significantly higher in HIV-1 infected males of younger ages of African ancestry compared to other ethnic groups. Analysis of HIV-1 patient datasets revealed that Kaiso might have a role in HIV infection and replication in African Native patients through different immune system genes and its association with multiple intermediary pathways. Moreover, a negative significant correlation between Kaiso expression and CD4+ T cell count and this may correlate the depletion of CD4+T cells in HIV-1 infection with Kaiso expression, additionally, our analysis showed a positive correlation between Kaiso expression and HIV viral load that was higher in African ancestry compared to US patients. Taken together, we suggest that Kaiso may act as a novel therapeutic agent in HIV1 infection.

Further studies to analyze the role of Kaiso in other HIV-1 infected groups needed, such as elite controllers, and to investigate the role of Kaiso in association with expression of different immune system genes.

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