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Research Article

Association of KIR haplotypes with propensity for developing chronic hepatitis B induced liver diseases (cirrhosis and hepatocellular carcinoma) and HIV-1 infection in a West African Cohort

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Abstract

Objectives: A subset of specialized KIR haplotype has been shown to be strongly associated with susceptibility or resistance to viral infections in humans. Therefore, this pilot investigation sought to determine the frequencies of KIR Haplotype in hepatitis B (HBV) and HIV-1 infected patients and their clinical impacts in disease progression and staging in Burkina Faso.

Methods: Hepatitis B infected patients, Human Immunodeficiency virus type 1 (HIV-1) infected individuals and healthy individuals were selected for this study. Hepatitis B surface antigen (HBsAg), anti-HCV antibodies and anti-HIV-1/2 antibody/antigen were screened using a 4th generation ELISA assay (ARCHITECT I 1000SR®TM, Abbott Laboratories, USA). In addition, SSP-PCR was used to search the frequencies of KIR haplotype. HBV viral load and HIV-1 viral load was determined in patients along with the CD4+ count.

Results: A and B KIR haplotypes was found to be associated with protection against HBV chronic infection evolution to cirrhosis (OR= 0.17, CI95% = 0.03-0.80, *P*= 0.03) and Hepato-Cellular Carcinoma (HCC) (OR= 0.32, CI95% = 0.11-0.92, *P*= 0.04). No association was found between markers of HIV infection and KIR haplotypes. No difference was found with regard to the Viral Load of HBV, HIV-1 and KIR haplotype.

Conclusion: Our results suggest that A and B KIR haplotypes was associated with protection against HBV chronic infection evolution to cirrhosis and/or HCC. KIR haplotypes do not seem to be associated with immunosuppression status among HIV positive person. Further investigations are in need to fully understand the clinical significance of KIR Haplotype in HBV, HIV disease progression to improve patient's managements in Burkina.

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Introduction

Hepatitis B Virus (HBV) and Human Immunodeficiency Virus (HIV) infections can progress to chronic hepatitis B and AIDS respectively. Chronic Hepatitis B infection seems to be a risk factor for the development of cirrhosis and Hepatocellular Carcinoma in Africa (HCC).

The overall cancer incidence in 2018 was 18.1 million new cases. But according to International Agency for Research on Cancer (IARC), in 2040, this incidence will increase to 29.5 million [1]. Most of these cancer cases are predominantly found in developing countries, such as Burkina Faso. Cancer causing infections like hepatitis and Human Papillomavirus (HPV) are responsible of approximately 25% of cancer cases in low and middle-income countries [2]. HCC can develop on an apparently healthy liver or on a cirrhotic liver and cirrhosis is often present as a post-hepatic infection in patient from Africa. However, despite therapeutic progress, HCC remains a serious public health problem because of its high mortality rates. In Burkina Faso, liver cancer is the third most common cancer in terms of incidence with 1,296 new cases in 2018 [1]. This is the first cancer in male.

After almost four decades of fighting HIV/AIDS, it remains a public health concern in Burkina Faso and in the rest of the world. With the increase in the number of people receiving antiretroviral drugs in a context of limited resources, we are gradually seeing a comparable improvement in life expectancy of HIV-infected people in resources limited countries. In Burkina Faso, the last decade has seen a drastic decline of HIV prevalence and the number of individuals living with HIV was estimated at 95,000 in 2017 [3].

It has been demonstrated that HIV and HBV infections are influenced by host genetic factors.

Among these genetic factors, the killer cell immunoglobulin-like receptors (KIRs) have been shown modulate the effector functions of Natural Killer (NK) cells during viral infections and against tumorigenic cells. In adults, NK cells account for 5%-20% of circulating blood cells and represent a major cellular component of the innate immune system. They act by direct identification and elimination of abnormal target cells including infected cells and cancer cells. So far, two KIR haplotypes have been identified (haplotypes A and B). The number and composition of KIR genes varies from one individual to another. Class A haplotypes are generally characterized by the presence of inhibitory genes (KIR2DL4 and KIR2DS4), and most KIR2DS4 alleles have an exon deletion, which renders them non-functional [4]. Class A haplotypes are structurally invariant (consisting of one gene-content haplotype and its deleted forms) and allelic polymorphic. Conversely class B haplotypes are characterized by relatively little allelic polymorphism but greater structural diversity, as they display various combinations of all KIR genes [4]. These two classes are in balancing selection, while class A haplotypes is associated with protection against viral infection, class B haplotypes is usually linked with reproductive advantages as well as other unknown functions [5]. However, very little is known on the association between KIR haplotypes and chronic HBV and HIV infection in Sub-Saharan Africa, particularly in Burkina Faso. Thus, the present study was undertaken to i) determine whether or not KIR haplotypes were associated with susceptibility to develop liver cirrhosis and hepatocellular carcinoma following chronic HBV infection and (ii) investigate the association of KIR haplotypes with HIV progression in HIV-1 positive patients from Burkina Faso, West Africa.

Methods

This was prospective and case-control studies conducted from January to September 2017 and from January to June 2019. A total of 389 individuals were included in this investigation, which consisted of 110 HBV chronic patients, 145 HIV-1 infected patients and 134 seronegative individuals (HBV, HIV-1, HCV negative) recruited at the Pietro Annigoni Biomolecular Research Center (CERBA/LABIOGENE) and the regional blood transfusion center of Ouagadougou (CRTS/O), respectively. Blood samples were collected from HBV and HIV-1 infected patients and from healthy voluntary and non-remunerated blood donors at CRTS/O. Serological tests using four-generation ELISA Ag/Ab were performed for HIV, HCV and HBV screening and confirmation in the control group using the Cobas e 411 Analyzer (Roche Diagnostics GmH Mannheim, Germany) according to the manufacturer's protocol. Serological markers for HIV-1 and HCV of HBV infected patients were detected and serological markers for HBV and HCV of HIV-1 infected patients were detected using HIV Human Immunodeficiency Virus Rapid Test Device (Abon Biopharm Guangzhou, Co., Ltd Chine), HBV One Step Hepatitis B Virus Combo Test Kits (Abon Biopharm Guangzhou, Co., Ltd. China) and HCV Hepatitis C Virus Rapid Test Device (Abon Biopharm Guangzhou, Co., Ltd Chine), respectively to rule out possible cases of infection with these viruses. This was previously described by Sorgho, et al. [6,7]. Samples collection, measurement of HBV, HCV and HIV viral markers as well as and quantification of lymphocytes TCD4, HIV-1 and HBV viral load quantification, DNA extraction and KIR genotyping were also previously described by the same authors [6,7].

KIR genes analysis

KIR Haplotypes genes were amplified using the SSP-PCR (Sequence Specific Primer PCR) method as previously described [8]. The samples were classified into 3 groups corresponding in three genotypes (AA, AB and BB), based on the content of the KIR gene, into two groups of haplotype A and B. Haplotype A is defined by the absence of genes associated with haplotype B (2DL2, 2DL5, 3DS1, 2DS1, 2DS2, 2DS3, 2DS5). Individuals without these genes associated with haplotype B are considered to be homozygous for haplotype A and therefore assigned to the genotype AA. The absence of one or more genes associated with haplotype A (2DL1, 2DL3, 3DL1 and 2DS4) defines a homozygous individual of haplotype B, of genotype BB. The A and B genotypes have both all of the haplotype A specific genes and one or more of the haplotype B specific genes [9].

Statistical analysis

Statistical analyzes were performed using Microsoft Office Excel 2019 and Epi Info 7 software. *P*-values <0.05 were

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considered statistically significant. Association between KIR haplotype and HIV-1 or HBV infection was established by comparing frequencies between cases and controls using the $\chi 2$ test. The Odd Ratio (OR) and 95% Confidence Intervals (CI) were calculated to estimate the associations between KIR Haplotypes and infections.

Ethical aspects

This investigation was approved by the National Health Ethic Committee of Burkina Faso (reference number N° 2017-01-004). Patients' written and informed consents were obtained according to the Helsinki Declarations. All results were used as parameters in the therapeutic management of patients.

Results

Socio-demographic and clinical characteristics of the study patients. Among HBV positive people, 74(67.27%) had chronic HBV infection, 8(7.27%) had liver cirrhosis and 26(23.64%) had HCC. HBV positive and negative controls did not differ by sex but with age. We found more people with an age >30 years in HBV positive compared to the control group. In HIV-positive people compared to HIV-negative controls, age and sex was statistically different (Table 1).

There was no statistically significant difference between KIR haplotypes and HBV viral load. On the other hand, when comparing the KIR haplotypes with the types of liver disease, we found that the AB genotype was more common in people with chronic infection compared to those with liver cirrhosis. This was similar for chronic infection compared to those with HCC (Table 2).

No association was found between markers of HIV-1 infection and KIR haplotypes. No difference was found with regard to the VL<1000IU/mL_CD4 group's ≥500IU/mL and VL≥1000IU/mL_CD4 <500IU/mL (%). KIR haplotypes do not seem to be associated with immunosuppression status among the HIV-1 positive person (Table 3).

Discussion

This is the first study documenting the association between KIR haplotypes and HBV, HIV-1 infection and

Table 1: Socio-demographic and clinical characteristics of the study patients.

Variable		Comparison of HBV+ and controls				Comparison of HIV+ and controls			
		HBV+ N(%)	Controls N(%)	OR(CI95%)	*p* value	HIV+ N(%)	Controls N(%)	OR(CI95%)	*p* value
Sex	Male	59(53.64)	60(44.78)	1.42(0.85-2.36)	0.1	44(30.34)	60(44.78)	0.53 (0.32-0.87)	0.01
	Female	51(46.36)	74(55.22)			101(69.66	74(55.22)		
	Total	110	134	-	-	145	134	-	-
Age(years)	≤ 30 years	37(33.64)	78(58.21)	0.36 (0.21-0.61)	<0.001	8(5.52)	78(58.21)	0.04 (0.02-0.09)	<0.001
	> 30 years	73(66.36)	56(41.79)			137(94.48)	56(41.79)		
	Total	110	134	-		145	134	-	-
Co-infection HBV/HIV	Yes	0(0.0)	0(0.0)	-	-	9(6.21)	0(0.0)	-	-
	No	0(0.0)	0(0.0)	-	-	136(93.79)	0(0.0)	-	-
	Total	110	134	-	-	145	134	-	

Table 2: HBV markers or liver disease versus KIR Haplotypes.

KIR Haplotype	AA	AB	BB	Total
HBV Viral Load				
VL< 2000 IU/mL N(%)	18(28.57)	12(19.05)	33(52.38)	63(100)
VL ≥2000 IU/mL N(%)	14(29.79)	14(29.79)	19(40.43)	47(100)
	OR(CI95%) = 1.06(0.46-2.43) *p*= 1	OR(CI95%) = 1.8(0.74-4.37) *p*= 0.2	OR(CI95%) = 0.61(0.28-1.32) *p*= 0.2	-
HBV Chronic infection versus cirrhosis				
HBV Chronic infection N(%)	25(33.78)	11(14.86)	38(51.35)	74(100)
Cirrhosis N(%)	1(12.5)	4(50.00)	3(37.5)	8(100)
	OR(CI95%) = 3.57(0.41-30.66) *p*= 0.4	OR(CI95%) = 0.17(0.03-0.80) *p*= 0.03	OR(CI95%) = 1.75(0.39-7.90) *p*= 0.7	-
HBV Chronic infection versus HCC				
HBV Chronic infection N(%)	25(33.78)	11(14,86)	38(51,35)	74(100)
HCC N(%)	6(23.08)	9(34,62)	11(42,31)	26(100)
	OR(CI95%) = 1.70(0.60-4.77) *p*= 0.4	OR(CI95%) = 0.32(0.11-0.92) *p*= 0.04	OR(CI95%) = 1.43(0.58-3.54) *p*=0.5	-
Cirrhosis versus HCC				
Cirrhosis N(%)	1(12.5)	4(50.00)	3(37.5)	8(100)
HCC N(%)	6(23.08)	9(34.62)	11(42.31)	26(100)
	OR(CI95%) = 0.47(0.04-4.68) *p*= 1	OR(CI95%) = 1.88(0.37-9.39) *p*= 0.6	OR(CI95%) = 0.81(0.16-4.17) *p*= 1	-

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Table 3: HIV-1 markers versus KIR Haplotypes.

KIR Haplotype	AA	AB	BB	Total
HIV-1 Viral Load				
VL< 1000IU/mL N(%)	21(15.67)	21(15.67)	92(68.66)	134(100)
VL ≥ 1000IU/mL N(%)	2(18.18)	1(9.09)	8(72.73)	11(100)
	OR(CI95%)= 1.19(0.24-5.93) *p*= 1	OR(CI95%)= 0.53(0.06-4.42) *p*= 0,2	OR(CI95%)= 1.21(0.30-4.82) *p*= 0,2	-
CD4+				
CD4<500IU/mL N(%)	6(11.11)	6(11.11)	42(77.78)	54(100)
CD4≥500IU/mL N(%)	17(18.68)	16(17.58)	58(63.74)	91(100)
	OR(CI95%)= 0.5(0.20-1.47) *p*= 0.2	OR(CI95%)= 0.58(0.21-1.60) *p*= 0.3	OR(CI95%)= 1.99(0.92-4.30) *p*= 0.1	-
Viral load and CD4+				
VL<1000IU/mL and CD4 ≥ 500IU/mL N(%)	17(18.68)	16(17.58)	58(63.74)	91(100)
VL ≥ 1000 IU/mL and CD4< 500 IU/mL N(%)	2(18.18)	1(9.09)	8(72.73)	11(100)
	OR(CI95%) = 0.96(0.19-4.88) *p*= 1	OR(CI95%) = 0.46(0.05-3.92) *p*=0.6	OR(CI95%) = 1.51(0.37-6.11) *p*= 0.7	-

disease progression in patients from Burkina Faso. Chronic HBV infection is the most common of HCC and cirrhosis related mortality in developing countries [10]. Human Immunodeficiency Virus (HIV) continues to be a public health in sub-Saharan Africa. Decades of fight against and availability of antiviral therapy in Africa have helped decreased HIV incidence and mortality. Despite all of these efforts, recently new HIV cases were reported in the continent [3]. Very little is known on the genetic basis of chronic HBV induced liver cancer and HIV infection in Burkina Faso, particularly the role of KIR haplotypes in disease progression, persistence and chronicity. Therefore, this study was conducted to remedy at the paucity of data on frequencies of KIR haplotypes among patients with chronic HBV induced cirrhosis, Hepatocellular Carcinoma (HCC) and HIV infection.

The goal is to use these findings to develop effective strategies to improve the clinical management of HBV and HIV patients in the country. Among the cohort of HBV positive patients, 67.27% had chronic HBV infection, 7.27% had liver cirrhosis and 23.64% had HCC. The majority of HBV+ individuals were among the age group >30 years.

In HIV-1 positive subjects, women were more infected than men with significant differences recorded when comparing age and gender (Table 1). Due to the high proportion of women in HIV-1 infected patients, some studies suggested that women had an increasing risk of being infected by HIV than men. According to World health organization, Women are more likely to be infected with HIV in any type of sexual intercourse than men because of biological factors, such as frequent exposure of the mucosal areas during sexual intercourse [11]. Moreover some, countries like Burkina Faso, through the prevention of mother to child program of HIV infection, HIV testing for all pregnant women is recommended and routinely implemented. The proportion of HIV-1 positive patients aged >30 years was higher than that of those with age <30 years (94.48% versus 5.52%). Decrease in HIV-related mortality since the introduction of combination antiretroviral therapy has resulted in increased life expectancy and an aging HIV positive population [12].

There were no statistically significant differences between KIR haplotypes and HBV viral load. On the other hand, when comparing the KIR haplotypes with liver diseases, it was found that the A and B genotypes are more common in people with chronic infection compared to those with liver cirrhosis (*P*= 0.03). This is the same finding for chronic infection compared to those with HCC (Table 2). The A and B genotypes was associated with the protection of evolution of chronic HBV to cirrhosis and primary liver cancer. They have both all of the haplotype A specific genes and one or more of the haplotype B specific genes. The KIR A haplotypes contains mostly inhibitory KIR genes, whereas KIR B haplotypes contain more activating KIR loci [13]. Zhiming Lu, et al. found that the frequency of haplotype B was higher in patients with chronic hepatitis B and Sero-reconversion controls compared with healthy controls. The combinations of Human Leukocyte Antigen (HLA) and KIR genes have been associated with autoimmunity, viral infections, reproductive failure and cancer [14-19]. In human populations, there is a variable balance between group A and group B KIR haplotypes, which appears to be maintained by balancing selection for inhibitory and activating functions [20,21]. This selection is mediated, in part, by the interaction of inhibitory KIR with their HLA class I ligands. Because of the biologic significance of the A/B haplotype difference, it is believed that A and B haplotypes could influence HBV infection and HBV clearance. Activating and inhibiting KIRs could act simultaneously to destroy infected cells and cancer cells. Non-infected and healthy cells expressing HLA class I proteins are preserved through inhibitory "self-recognition" mechanisms that prevent their lysis, whilst infected cells and cancer cells lacking the HLA class I molecules on their surfaces are recognized and lysed through interaction with activating receptors [22]. However, no association was found between the markers of HIV infection and KIR haplotypes. KIR haplotypes do not seem to be associated with immunosuppression among HIV-positive individuals in this study. Win jennes, et al. found that group B KIR haplotypes and lack of specific inhibitory KIR ligand genes, genotypes considered to favor NK cell activation, are predictive of HIV-1 disease progression [23]. However, the main limitations of this study are that only KIR haplotype

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characterization, but not KIR/HLA combination. Thus, further research with more samples is required to uncover the molecular mechanisms by which KIR haplotype contribute to the infection and clearance of HBV and HIV.

Conclusion

These results suggest that AB KIR haplotype is associated with protection against HBV chronic infection, thereby disease evolution to cirrhosis and PLC among patients from Burkina Faso. Since no association was found between KIR haplotype and HIV infection. Our findings might be useful for predicting the precision medicine in HBV patients, AB KIR haplotype could as an immunogenic marker in the gene therapy and additional investigations on KIR/HLA interactions are needed to fully comprehend the various molecular mechanisms governing KIR genes involvement to HBV, HIV infection to improve patient outcomes.

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