Interferon lambda 3/4 polymorphisms are associated with AIDS-related Kaposi's sarcoma

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Background: Kaposi's sarcoma, the most common AIDS-related cancer, represents a major public concern in resource-limited countries. Single nucleotide polymorphisms within the Interferon lambda 3/4 region (IFNL3/4) determine the expression, function of IFNL4, and influence the clinical course of an increasing number of viral infections.

Objectives: To analyze whether *IFNL3/4* variants are associated with susceptibility to AIDS-related Kaposi's sarcoma among MSM enrolled in the Swiss HIV Cohort Study (SHCS).

Methods: The risk of developing Kaposi's sarcoma according to the carriage of *IFNL3/4* SNPs *rs8099917* and *rs12980275* and their haplotypic combinations was assessed by using cumulative incidence curves and Cox regression models, accounting for relevant covariables.

Results: Kaposi's sarcoma was diagnosed in 221 of 2558 MSM Caucasian SHCS participants. Both *rs12980275* and *rs8099917* were associated with an increased risk of Kaposi's sarcoma (cumulative incidence 15 versus 10%, $P = 0.01$ and 16 versus 10%, $P = 0.009$, respectively). Diplotypes predicted to produce the active P70 form (cumulative incidence 16 versus 10%, $P = 0.01$) but not the less active S70 (cumulative incidence 11 versus 10%, $P = 0.7$) form of IFNL4 were associated with an increased risk of Kaposi's sarcoma, compared with those predicted not to produce IFNL4. The associations remained significant in a multivariate Cox regression model after adjustment for age at infection, combination antiretroviral therapy, median $CD4^+$ T-cell count

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nadir and $CD4^+$ slopes (hazard ratio 1.42, 95% confidence interval 1.06–1.89, $P = 0.02$ for IFLN P70 versus no IFNL4).

Conclusion: This study reports for the first time an association between *IFNL3/4* polymorphisms and susceptibility to AIDS-related Kaposi's sarcoma.

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Keywords: AIDS, HIV, interferon lambda 3, immunogenetics, Kaposi's sarcoma, polymorphism

Introduction

Kaposi's sarcoma was initially described by Moritz Kaposi [1] in 1872 as a rare and relatively indolent angioproliferative neoplasm affecting elderly men from countries surrounding the Mediterranean Sea (classical form of Kaposi's sarcoma). Another form was described in sub-Saharan Africa in the 1950s, which affects middle aged adults and children (endemic form of Kaposi's sarcoma) [2]. In 1981, a potentially fatal form of Kaposi's sarcoma was described among young homosexual men as a characteristic feature of the AIDS epidemics (epidemic form of Kaposi's sarcoma), a population in which it still represents one of the most common AIDS-related cancer [3–8]. An invasive form can also affect patients with non-AIDS immune suppression, in particular, solid organ transplant (SOT) recipients (iatrogenic form of Kaposi's sarcoma, reviewed in [2]).

Although the four epidemiological forms of Kaposi's sarcoma share the same histological characteristics [9] and are all subsequent to human herpes virus 8 (HHV-8) infection [10,11], the development of distinct clinical features seems to rely on a combination of host and environmental factors. Although HIV-related or drug-related immune suppression is inherent to the epidemic and iatrogenic forms (AIDS and SOT), genetic predisposition may be required for the classical (Mediterranean and Jewish ancestry) [12–14] and endemic forms (sub-Saharan Africa) [15]. Hormonal factors [16–19] have been proposed to explain the male predominance of all forms of Kaposi sarcoma. Environmental conditions relative to potential routes of infection (soil, animal vectors) have been proposed to influence susceptibility to different forms of Kaposi's sarcoma [20–25]. Although viral factors may influence clinical presentation, evidence for a definite link between a specific subtype strain and a Kaposi's sarcoma type is still lacking [26–29].

Several investigators have analyzed the role of host genetic factors in susceptibility to Kaposi's sarcoma within a given population at risk. The most relevant was a polymorphism within the *IL-6* promoter, which was consistently more frequent among Kaposi's sarcoma patients versus controls in two cohorts of AIDS patients [30,31] and a small cohort of SOT patients [32]. Polymorphisms in other candidate genes (e.g. MHC-related or cytokines/chemokines-related genes) were associated with Kaposi's sarcoma in studies of AIDS patients [31,33–35] and two studies including patients with the classical form of Kaposi's sarcoma [36,37].

Single nucleotide polymorphisms (SNPs) in the region encoding for interferon lambda 3 (IFNL3 previously named IL-28B) and interferon lambda 4 (*IFNL4*) represent major factors in the ability of individuals to clear hepatitis C virus (HCV) [38–41]. They determine different haplotypic combinations (diplotypes) based on their capacity to produce IFNL4, that is, no production versus production as an active P70 or less active S70 form [42–44]. *IFNL3/4* SNPs are increasingly known to influence the susceptibility to or the clinical course of infections due to viruses other than HCV, including herpes viruses such as cytomegalovirus (CMV) and Epstein–Barr virus (EBV) [45–47]. Here, we hypothesize that *IFNL3/4* polymorphisms influence the risk of AIDS patients to develop Kaposi's sarcoma.

Material and methods

Study patients

The Swiss HIV Cohort Study (SHCS) is an ongoing multicenter prospective study of HIV-infected patients enrolled at seven major Swiss hospitals and their local affiliated centers since 1988 [48]. For the present study, Caucasian MSM with available DNA for genotyping and a written informed consent for genetic studies were included. In order to account for the time at risk, only patients with an estimated date of HIV infection were selected [49]. Demographic characteristics including age, duration of HIV infection, $CD4^+$ T-cell count nadir, other opportunistic infections, HIV maximal viral load and HAART use were extracted from the SHCS clinical database. Kaposi's sarcoma was defined according to predefined clinical and histological criteria.

Single nucleotide polymorphism genotyping

Genomic DNA isolated either from blood or cell pellets was genotyped for haplotype tagging SNPs *rs8099917* and *rs12980275* using a customized GoldenGate

Genotyping Assay on Veracode platform (Illumina , San Diego, California, USA). These SNPs were used as surrogates for rs368234815 and rs117648444, respectively, based on previously published linkage disequilibrium (LD) values, which were shown to determine the three main diplotypic forms of IFNL4.

Statistical analysis

Statistical analyses were performed using Stata (version 14.2, StataCorp LP, College Station, Texas, USA). Hardy–Weinberg equilibrium (HWE) was verified using the program genhw implemented in Stata. Haplotypes were inferred using Phase and grouped according to their ability to express the different forms of IFNL3/4 as described previously [43]. The association of *IFNL3/4* polymorphisms with Kaposi's sarcoma was assessed by 25-year cumulative incidence curves as well as univariable and multivariable Cox regression models, using the estimated date of HIV infection as a starting point, with censoring at death and/or lost follow-up. The proportional hazard assumption was verified by using the stphtest command implemented in Stata. Estimated dates of HIV infection and $CD4^+$ slopes in both incident and prevalent cases were obtained by using a joint back calculation model as described previously [50].

Results

The study included 2558 MSM patients among whom 221 developed Kaposi's sarcoma (8.6%, Supplementary Table 1, http://links.lww.com/QAD/B360). Considering the whole patient population, the median age at estimated date of HIV infection was 34 (interquartile range, IQR = 13). The median $CD4^+$ T-cell nadir was 181 cells/mm^3 (IQR = 174) and the maximal HIV RNA viral load 5.12 $\log_{10}$ copies/ml (IQR = 0.85). Most individuals started HAART therapy during follow-up (97%). An active HBV infection was recorded in 10% of patients and HCV serology was positive in 8%.

The minor allele frequencies (MAFs) of IFNL3/4 *rs12980275* and *rs8099917* were 0.30 and 0.20, respectively, and both were at HWE. Carriage of *rs12980275* and *rs8099917* were both associated with an increased risk of Kaposi's sarcoma (cumulative incidence 15 versus 10%, $P = 0.01$ and cumulative incidence 16 versus 10%, $P = 0.009$, respectively, Fig. 1). Diplotypes predicted to produce the active P70 form of IFNL4, but not those predicted to produce the less active S70 form were associated with an increased risk of Kaposi's sarcoma, compared with diplotypes not producing IFNL4 (cumulative incidence 16 versus 10%, $P = 0.01$ and cumulative incidence 11 versus 10%, $P = 0.7$, respectively).

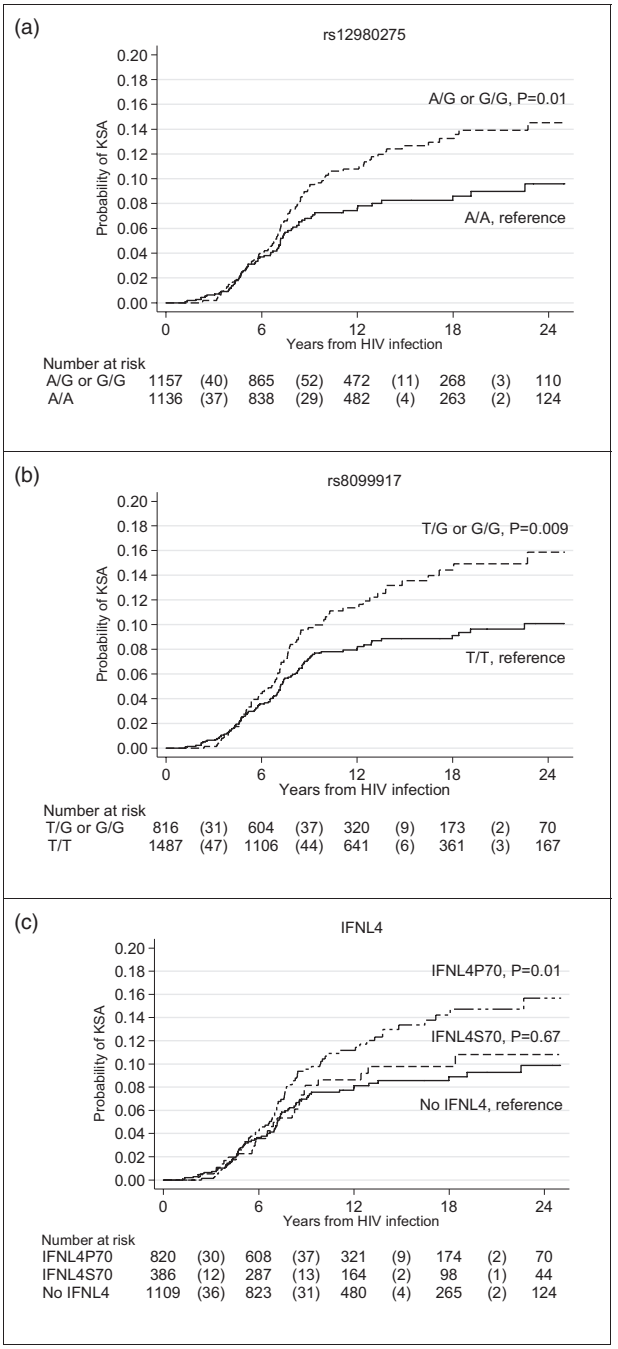

Fig. 1. Cumulative incidence of Kaposi's sarcoma according to IFNL4 *rs12980275* (a), IFNL3/4 *rs8099917* (b), IFNL4 diplotypes (c) in MSM participants of the Swiss HIV Cohort Study. The estimated date of HIV infection was used as a starting point with censoring at death or lost follow-up. Numbers in parenthesis indicate the number of patients with Kaposi's sarcoma in each group of patients. *P* values were calculated by log-rank test, dominant mode.

The association between IFNL4P70-producing diplotypes and Kaposi's sarcoma remained significant in a multivariate Cox regression model, accounting for age at infection, HAART, median $CD4^+$ T-cell count nadir and

Table 1. Independent risk factors associated with Kaposi's sarcoma among MSM.

Variable	Univariate		Multivariate	
	Hazard ratio (95% CI)[a]	*P*	Hazard ratio (95% CI)	*P*
Age at estimated date of infection[b]	1.01 (1.00–1.03)	0.07	1.01 (1.00–1.03)	0.04
$CD4^+$ nadir (<200 cells/mm^3)	2.56 (1.87–3.51)	<0.001	2.02 (1.45–2.82)	<0.001
$CD4^+$ slope[c] (continuous)	0.69 (0.58–0.81)	<0.001	0.71 (0.60–0.85)	<0.001
Maximal HIV RNA load (continuous)	1.21 (1.01–1.44)	0.04		
HAART (time-dependant covariate)	0.43 (0.31–0.60)	<0.001	0.36 (0.25–0.51)	<0.001
HCV co-infection[d]	0.92 (0.55–1.53)	0.75		
Active HBV infection[e]	1.32 (0.78–2.24)	0.30		
SNPs				
IFNL3/4 rs12980275 (AA versus AG or GG)	1.36 (1.04–1.77)	0.03		
IFNL3/4 rs8099917 (TT versus TG or GG)	1.40 (1.07–1.82)	0.01		
Diplotypes				
No IFNL4	Reference		Reference	
IFNL4 P70	1.40 (1.05–1.87)	0.02	1.42 (1.06–1.89)	0.02
IFNL4 S70	1.09 (0.74–1.61)	0.67	1.11 (0.75–1.64)	0.61

CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus.
[a]The proportional hazard assumption was verified for all variables with the exception of $CD4^+$ slope. However, the association between IFNL4P70 and Kaposi's sarcoma was similar when $CD4^+$ slope was removed from the multivariate model (hazard ratio 1.33, 95% CI 1.07–1.65, $P = 0.01$).
[b]Per 1 year.
[c]Rate of $CD4^+$ depletion in the absence of HAART.
[d]Reflected by HCV serology.
[e]Defined by the presence of HBsAg in the blood.

$CD4^+$ slopes (hazard ratio 1.42, 95% confidence interval (95% CI) 1.06–1.89, $P = 0.02$; Table 1).

Discussion

Polymorphisms in the region encoding for IFNL3 and 4 have been identified for their major role in the ability of individuals to clear HCV. Increasing evidence suggests that such polymorphisms can also influence the clinical course of infections due to viruses other than HCV [51,52], in particular those from the Herpesviridae family [CMV [45,46], EBV [47] and herpes simplex virus (HSV) [53]]. In this study, we report for the first time an association between *IFNL3/4* polymorphisms and susceptibility to Kaposi's sarcoma among HIV-infected MSM.

An increasing number of in-vitro studies support the role of IFNL in the immunopathogenesis of viral infections due to viruses other than HCV. A series of cell culture-based models have shown that IFNL3/4 controls the replication of viruses such as human [54] and murine CMV [55], HSV2 [56], HBV [57], dengue virus [58], human metapneumovirus (hMPV) [59], influenza virus [60–62], lymphocytic choriomeningitis virus (LCMV) [63] and Sendai virus [64]. Although no studies have analyzed the direct role of IFNL on HHV-8 replication, the involvement of IFNL in its immunopathogenesis is supported indirectly by at least two studies. Those showed that HHV-8 can inhibit interferon transcription by the production of interferon regulatory factor (IRF) homologues as well as block the expression of interferon-stimulating genes (ISGs) through Janus kinase-signal transducer and activator of transcription pathway interference [65,66].

Haplotypic combinations predicted to produce the P70 active, but not the S70 less active form of IFNL4, were associated with an increased risk of Kaposi's sarcoma. This is consistent with the association reported in other viral infections; SNPs encoding or tagging the P70 form of IFNL4 induce a higher susceptibility to HCV [42,44], CMV [45,46], EBV [47] and HSV [53]. This paradoxical effect of IFNL4 may rely on at least three different mechanisms. First, IFNL4 may compete with the other IFNLs through a mechanism involving the overexpression of its IFNLR1 subunit [67]. Second, IFNL4 may induce a refractory state of the pathway because of persistent ISG expression [43]. Third, individuals expressing the active form of IFNL4 may in return produce lower amount of IFNL3, with subsequent reduced ISG expression [42,68,69]. The resulting balance between IFNL3 and IFNL4 expression may be particularly relevant in Kaposi's sarcoma lesions, given the presence of numerous recruited plasmacytoid dendritic cells (pDC), which represent the most important producer of these cytokines [70].

Beyond antiviral properties, IFNLs may also exert antitumoral activities including a growth inhibitory effect and apoptosis of tumor cells, as recently described in culture of melanoma [71], lung adenocarcinoma [72,73], neuroendocrine cancer [74], colorectal carcinoma [75], esophageal carcinoma [76] and hepatocellular carcinoma [77] cells or in mouse models of melanoma [78], colon adenocarcinoma [78] and fibrosarcoma [79]. In humans, the expression of IFNL1 has been negatively correlated

with the progression of cervical cancer because of papilloma virus [80], suggesting a potential role of this cytokine in cancer immunity. Altogether, these data suggest that polymorphisms in IFNLs may not only influence the immunity against HHV-8, but also the immunity against Kaposi's sarcoma cancer cells.

Like most genetic association studies, our study performed on HIV-infected MSM is constrained by some limitations. Data on HHV-8 seroprevalence are not available in the SHCS cohort, thereby preventing analyses limited to patients with Kaposi's sarcoma but excluding HHV-8-positive individuals who did not develop Kaposi's sarcoma. This limitation may be at least in part compensated by the fact that the prevalence of HHV-8 among MSM is elevated [81,82] and that the prevalence of Kaposi's sarcoma and HHV-8 is very well correlated in HIV-infected populations [83–85]. Most likely, the currently chosen analytic approach would underestimate but not overestimate the effect of IFNL polymorphisms.

In summary, our data show an association between *IFNL3/4* polymorphisms and the development of Kaposi's sarcoma among HIV+ MSM patients. This new finding confirms that IFNLs mediate antiviral responses against a growing range of viruses.

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Conflicts of interest

There are no conflicts of interest.

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Author's contributions

S.B. performed sample management, DNA extraction, candidate SNP genotyping, statistical analysis and wrote the manuscript. A.W. performed SNP genotyping for the SHCS patients and data management. P.T. contributed to statistical analyses. Members of the SHCS group including, P.E.T., E.B., H.F., H.F.G., M.H., L.K., M.O., J.F., M.C. were directly involved in the clinical care of SHCS patients and data acquisition. P.Y.B. designed the SHCS genetic project, obtained funding, supervised genotyping, performed data management and statistical analysis and wrote the manuscript. All authors critically revised the manuscript.

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Appendix

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