DECREASED EXPRESSION OF MUCOSAL TYPE I IFN RESPONSE IN HPV INFECTED MSM PATIENTS

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BACKGROUND

Among HIV-1 positive men who have sex with men (MSM), the extremely high incidence of HPV infection is strongly associated with an increased risk of squamous cell carcinoma of the anal canal (SCCA).

Although most HPV infections are thought to be spontaneously cleared, the persistence of high risk (HR)-HPV infection is the major risk factor for the development of high-grade anal dysplasia.

Of note, innate immunity pathways, especially those related to type I interferon (IFN-I) are involved in HPV recognition and clearance.

Through evasion strategies adopted to overcome the host immune defense and establish persistent infection, HPV might target different IFN-I genes in HIV-1 MSM patients.

AIM OF THE STUDY

The aim of the present study was to characterize the IFN-I role in the onset and persistence of anal HPV infection in HIV-1 infected MSM patients .

METHODS

Anal brushings were collected from 86 Caucasian MSM HIV-1 infected patients, on long-term antiretroviral therapy (ART), attending different units of Policlinic Umberto I Hospital in Rome.

Detection of HPV DNA and genotyping were performed by PCR and sequencing. Liquid-based cytology was used to assess anal cytological lesions.

The mRNA levels of IFN α, IFN β, IFN ε, IFN α receptor (subunits R1 and R2) in anal brushings, were measured by TaqMan RT–PCR. Data were analyzed by Mann–Whitney U test (unpaired data) and Wilcoxon signed-ranked test (paired data) using SPSS v.20.0 (IBM, Somers, NY, USA). Differences were considered statistically significant when $p<0.05$.

A multivariate analysis was performed by Fisher's exact test.

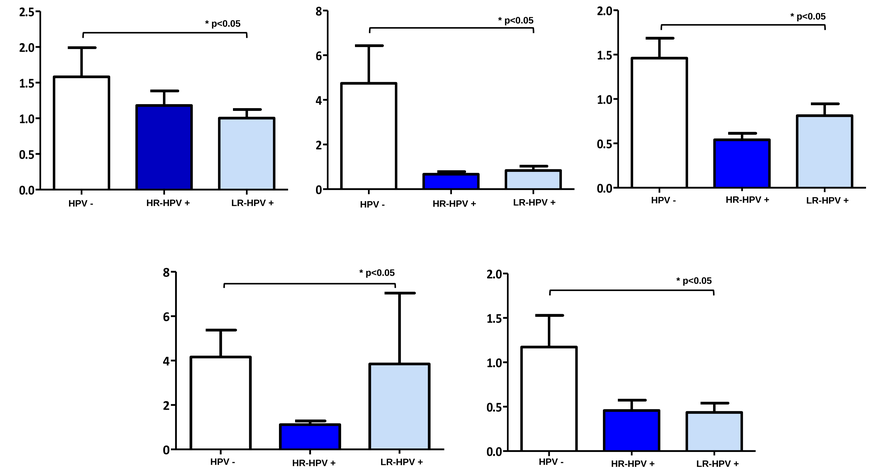
RESULTS

❖ Anal HPV DNA was detected in 71 MSM patients (83%), with 43% of the cases having a HR HPV genotype, mainly HPV16. Out of 86 patients, 54% showed high-grade squamous intraepithelial lesion (HSIL)/low-grade squamous intraepithelial lesion (LSIL).

❖ A decreased mucosal expression of IFN β, IFN ε, IFNAR1 and IFNAR2 was recorded in HR compared to low-risk (LR) HPV positive and HPV negative patients (Mann-Whitney U test, $p<0.05$ for all genes) (Figure 1). No differences were found on levels of IFN-I components according to the presence or absence of SIL.

❖ The expression of IFN β, IFN ε, IFNAR1 and IFNAR2 was reduced in patients with a persistent HPV infection (18%) compared to those who spontaneously cleared the infection (11%) after one years from baseline. [IFN β: 0.20 (IQR:0.05-0.52) vs 4.85 (IQR: 0.88-8.87); IFN ε: 0.36 (IQR: 0.04-1.53) vs 1.53 (1.07-1.84); IFNAR1: 0.82 (IQR: 0.5-1.56) vs 4.85 (IQR: 0.88-8.87); IFNAR2: 0.10 (IQR: 0.05-1.08) vs 4.65 (IQR: 1.31-7.56) ; ($p<0.05$ for all genes)].

Figure 1. Decreased IFN-I expression in High risk anal HPV positive HIV-1 infected MSM



Parameters	mRNA copies/mL	HPV infection Prevalence(%)	OR (CI 95%)	OR-adjusted (CI 95%)	p-value°
IFN α	<0.8	28(96%)	8.5(1.1-68)	8(1.2-66)	**<0.05**
	0.8 to 3	41(76%)	1.5(0.5-4)	1.6(0.5-4.1)	>0.05
	>3	2(100%)	1.5(0.0-35)	1.5(0.1-36)	>0.05
IFN β	<0.8	45(96%)	10.3(2.1-50)	10.4(2.2-50.1)	**<0.05**
	0.8 to 3	23(79.3%)	0.6(0.2-2.1)	0.6(0.2-2.0)	>0.05
	>3	3(33.3%)	0.0(0-0.28)	0.1(0.0-0.3)	**<0.05**
IFN ε	<0.8	44(9.7%)	21(2.6-171)	21.2(2.6-171)	**<0.05**
	0.8 to 3	24(64.8%)	0.0(0-0.3)	0.1(0-0.3)	**<0.05**
	>3	3(100%)	2.2(0.1-46)	2.2(0.1-47)	>0.05
IFNAR1	<0.8	34(94.4%)	5.5(1.1-26)	5.6(1.14-26.4)	**<0.05**
	0.8 to 3	34(85%)	1.2(0.4-3.9)	1.3(0.4-4)	>0.05
	>3	3(33.3%)	0.1(0.0-0.4)	0.1(0.1-0.5)	**<0.05**
IFNAR2	<0.8	49(87.5%)	2.2(0.6-7.1)	2.2(0.6-7)	>0.05
	0.8 to 3	22(81.4%)	1.1(0.3-3.4)	1.0(0.3-3.4)	>0.05
	>3	0(0%)	0.0(0-0.7)	0.1(0-0.8)	**<0.05**

❖A multivariate analysis showed that lower levels of IFN α, IFN β, IFN ε and IFNAR1 were associated with the presence of HPV infection observed in HIV-1 infected MSM ($p<0.05$). In addition, lower levels of IFN β, IFN ε, IFNAR2 and higher levels of IFNAR1 were associated a persistent HPV infection in HIV-1 infected MSM ($p<0.05$).

Parameters	mRNA copies/mL	HPV persistence Prevalence(%)	OR (CI 95%)	OR-adjusted (CI 95%)	p-value°
IFN α	<0.8	10(90.9%)	6(0.6-59)	6(0.7-60)	>0.05
	0.8 to 3	9(6%)	1.5(0.5-4)	1.6(0.5-4.1)	>0.05
	>3	1(100%)	1.1(0-31)	1.2(0.1-32)	>0.05
IFN β	<0.8	16(88.8%)	10.0(1.4-19)	10.0(1.4-71)	**<0.05**
	0.8 to 3	2(66.6%)	0.6(0-8.7)	0.6(0-8.7)	>0.05
	>3	2(33.3%)	0.0(0-1.3)	0.1(0-1.3)	>0.05
IFN ε	<0.8	16(88.8%)	10.0(1.4-71)	10.1(1.4-71)	**<0.05**
	0.8 to 3	4(44.4%)	0.6(0-8.7)	0.6(0.2-8.5)	>0.05
	>3	0(0%)	0.36(0.0-20)	0.4(0.1-18)	>0.05
IFNAR1	<0.8	10(83.3%)	6.0(0.6-59)	6(0.7-60)	>0.05
	0.8 to 3	9(90%)	2.0(0.3-13)	2.1(0.3-12)	>0.05
	>3	1(20%)	0.1(0-0.4)	0.1(0-0.4)	**<0.05**
IFNAR2	<0.8	16(80%)	3.0(0.5-19)	3.0(0.5-19)	**<0.05**
	0.8 to 3	3(75%)	0.4(0-3.4.1)	0.5(0-3.4.1)	>0.05
	>3	1(33.3%)	0.13(0-1.7)	0.13(0-1.7)	>0.05

CONCLUSIONS

HPV persistent infection may contribute to the downregulation of IFN-I response in vivo and contribute to the establishment of an immunosuppressive microenvironment in mucosal epithelia, which is essential for precancerous anal lesions progression.

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