Synergistic Effects of HIV, HPV, and Polyomaviruses on Interferon Response in Male Anal Mucosa

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BACKGROUND

Viral persistence is a crucial prerequisite for high-risk (HR) HPV-associated tumor growth, such as anal squamous cell carcinoma (SCC). Men living with HIV (MLWH) are more likely to be co-infected with HPV. Moreover, HIV may alter epithelial integrity, thereby favoring not only HPV but also Polyomaviruses (HPyVs) infections in basal cells, where they dysregulate cell division and local immunity. Indeed, HPyVs have garnered interest due to their carcinogenic potential and their possible presence in the anal mucosa, which could promote transmission through sexual intercourse. To explore the innate response of the anal mucosa in relation to HPV and HPyVs infections, we analyzed the expression of type I/III interferon (IFN) genes in anal cells from MLWH and non-MLWH.

METHODS

Sixty-one anal canal brushing samples were collected from men attending a proctology clinic. Detection of HPV and HPyVs [i. Merkel cell PyV (MCPyV), ii. JCPyV, iii. BKPyV] DNA was performed by PCR, and genotyping by sequencing. From purified cellular RNA, transcripts of genes encoding IFN-I (α, β), IFN-III (λ1-3), and TLR9 were measured by quantitative RT-PCR assays and normalized to the housekeeping GUS gene.

RESULTS

Thirty-five MLWH (mean age 47.7 years, SD 11.4), on long-term ART, and twenty-six controls (mean age 47.4 years, SD 15.3) were enrolled in this study. Out of the 61 men, 47 were HPV-positive, while 24 were HPyV-positive, with 87.5% specifically testing positive for MCPyV. HPV positive men showed decreased mRNA levels of TLR9 compared to the HPV-negative group. Furthermore, HPV/HIV co-infections and the presence of Low-grade Squamous Intraepithelial Lesion (LSIL) were associated with lower expression of TLR9 [Jonckheere-Terpstra test (JT), $p<0.05$)] (Fig. 1). IFN-I mRNA levels decreased in HPV-positive men [Mann-Whitney (MW) test, $p<0.05$] and even more in the HPV/HIV co-infections (IFN-α; JT, $p<0.01$) and HPV/HIV/HPyVs positive group (IFN-α; JT, $p<0.01$), compared to the negative ones (Fig. 2). HPV and HPV/HIV co-infections are associated with lower expression of IFN-III genes compared to the negative group (IFN-λ3, $p<0.05$). Differently, HPV/HIV/HPyVs co-infections induce higher IFN-III mRNA levels compared to the negative group (IFN-λ2; JT, $p<0.05$) (Fig. 3).

HPV positive men, HPV/HIV and HPV/HIV/HPyVs co-infections are associated with lower expression of TLR9 in male anal mucosa

HPV and even more HPV/HIV co-infections are associated with lower expression of IFN-I and IFN-III genes

HPV/HIV/HPyVs co-infections induce higher expression of IFN-III genes but are associated with lower expression of IFN-I genes

CONCLUSIONS

The findings highlight the potential synergy between HIV and HPV infections in compromising mucosal innate immunity and promoting viral co-infections, such as HPyVs, in the anal mucosa. Alterations in IFN and TLR-9 genes provide insights into complex mechanisms behind viral persistence, enhancing the understanding of innate immunity, viral infections, and HPV-related malignancies, with implications for future research and therapies.

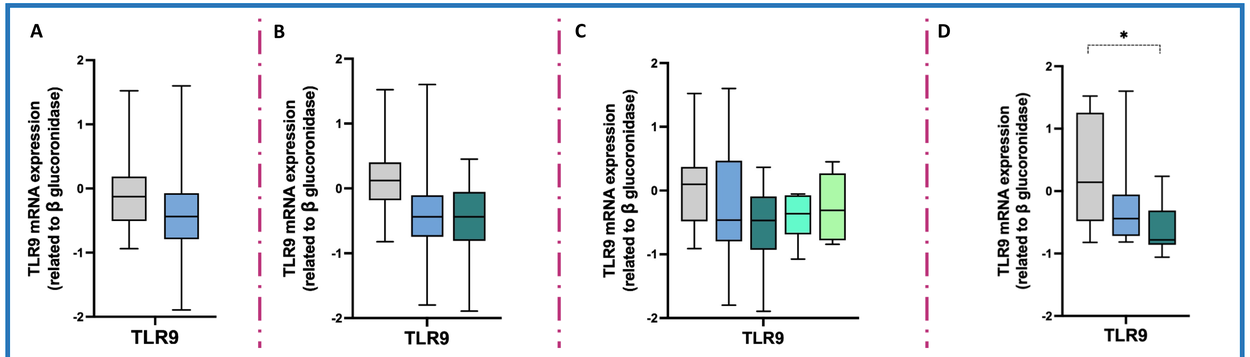

Fig. 1. Expression levels of TLR9 gene in HPV negative and HPV positive men (A), HPV/HIV negative, HPV positive and HPV/HIV positive men (B), HPV/HIV/HPyVs negative, HPV positive, HPV/HIV positive, HPV/HPyVs positive and HPV/HIV/HPyVs positive men (C), NOSIL/HPV/HIV negative, LSIL/HPV positive and LSIL/HPV/HIV positive men (*p<0.05).

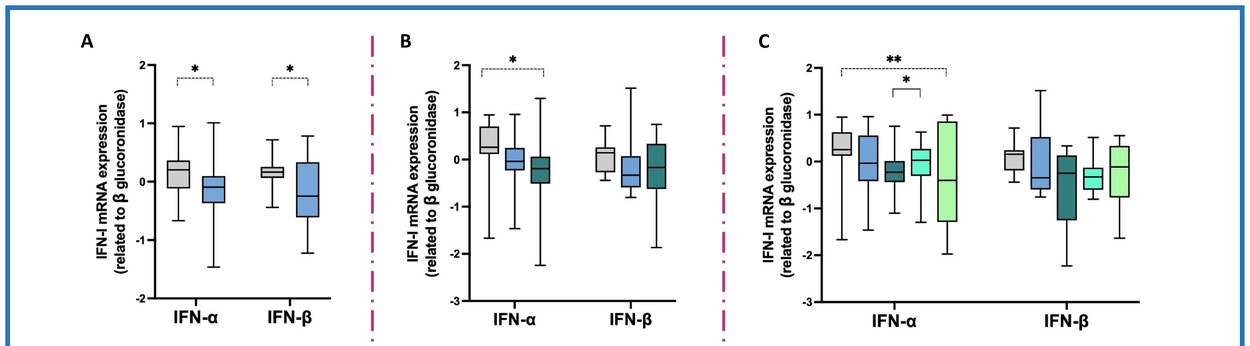

Fig. 2. Expression levels of IFN-I genes (IFN-α, IFN-β) in HPV negative and HPV positive men (A), HPV/HIV negative, HPV positive and HPV/HIV positive men (B), HPV/HIV/HPyVs negative, HPV positive, HPV/HIV positive, HPV/HPyVs positive and HPV/HIV/HPyVs positive men (C) (*p<0.05, **p<0.01).

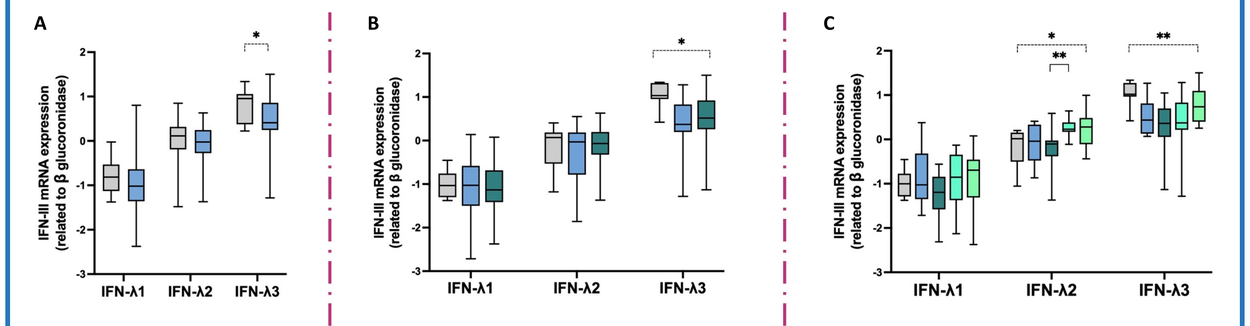

Fig. 3. Expression levels of IFN-III genes (IFN-λ1, IFN-λ2, IFN-λ3) in HPV negative and HPV positive men (A), HPV/HIV negative, HPV positive and HPV/HIV positive men (B), HPV/HIV/HPyVs negative, HPV positive, HPV/HIV positive, HPV/HPyVs positive and HPV/HIV/HPyVs positive men (C) (*p<0.05, **p<0.01).

HPV negative
HPV positive

HPV/HIV negative
HPV positive
HPV/HIV positive

HPV/HIV/HPyVs negative
HPV positive only
HPV/HIV positive
HPV/HPyVs positive
HPV/HIV/HPyVs positive