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Dys-regulated cross-talk between CD4+ T cells and NK cells in HIV/HCV co-infection

Benjamin Krämer*#, Andreas Glässner*#, Felix Goeser*#, Sebastian Diegeler*#, Pavlos Kokordelis*#, Marianne Eisenhardt*#, Franziska Wolter*#, Carolin Schwarze-Zander*# , Christoph Boesecke*#, Ulrich Spengler*#, Jürgen K. Rockstroh*#, and Jacob Nattermann*#.

* Department of Internal Medicine I, University of Bonn, Bonn, Germany # German Center for Infection Research (DZIF), Bonn, Germany

Contact:
benjamin.kraemer@ukb.uni-bonn.de
Phone: +4922828751415
Fax: +4922828751419

Background

HCV/HIV co-infection is associated with an accelerated progression of liver disease as compared to HCV mono-infection. Natural killer cells (NK cells) are considered to play an important role in hepatits C. Increasing data indicate that CD4+ T cells critically modulate NK cell activity. Dys-regulation of the CD4+ T cell pool is a hallmark of HIV infection. Thus, we speculated that an altered cross-talk between CD4+ T cells and NK cell might be involved in the immunopathogenesis of HIV/HCV o-infection.

Patients and Methods

40 HIV-infected patients, including 21 individuals that were HIV RNA(-) under HAART and 19 treatment-naïve HIV RNA(+) patients, as well as 20 healthy HIV(-)/HCV(-) controls were enrolled into this study. CD3/CD28 stimulated CD4+ T cells were analysed for IL-2 secretion by flow cyotmetry. Anti-viral activity of total PBMCs was studied using the HUH7-HCV-replicon system. IFN-g secretion and anti-HCV activity of NK cells was analyzed in the presence/absence of CD4+ T cells.

table 1: patient chracteristics

	HIV(+)		Healthy
	without HAART	with HAART	
Number	21	19	20
Male sex [%]	12 [57]	16 [84]	9 [45]
Age(years)	43	45	36
clinical data			
ALT	26,1	32,8	not measured
AST	23,0	25,2	not measured
HIV Status under HAART[%]	0	100	not measured
HIV viral load [copy RNA]	< 40	116567	not measured
CD4 cells/ µl	497,1	596,1	not measured
CD8 cells/ µl	957,6	1280,3	not measured

Conclusion

In conclusion, our data demonstrate that HIV infection has a strong suppressive effect on anti-HCV activity of NK cells which may contribute to low spontaneous clearance rate and accelerated progression of HCV-associated liver disease observed in HIV(+) patients.

Results

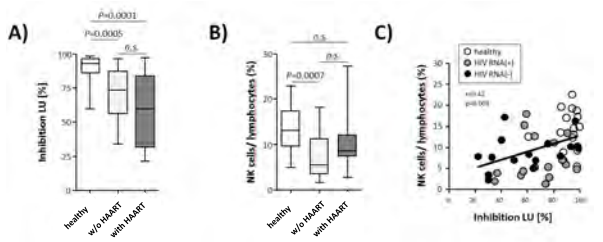


Figure 1. HIV infection is associated with impaired anti-HCV activity of NK cells.
Analysing inhibition of HCV replication, we found PBMC´s from HIV(+) patients to display a significantly lower anti-viral activity as compared to healthy controls, irrespective of HAART (Figure 1A).
Importantly, frequency of NK cells was positively correlated with PBMC-mediated blocking of viral replication (Figure 1C), indicating a role for NK cells in anti-HCV activity.
In this context, it is important to note that HIV RNA(+) individuals displayed significantly lower NK cell numbers than healthy controls ($p<0.0007$; Figure 1B), suggesting that HIV-induced decline in NK cell numbers might affect anti-HCV immune responses.
In HIV patients under effective HAART, however, NK cell frequency did not differ significantly from healthy controls (Figure 1B), indicating that additional functional alterations might be involved in the observed dys-regulated anti-viral activity.

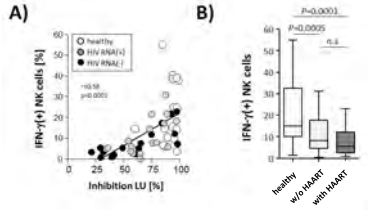


Figure 2. . HIV infection is associated with impaired IFNg production of NK cells.

Therefore, we next analysed NK cell IFN-g production, which was found to be positively correlated with PBMC-mediated inhibition of HCV replication (Figure 1A). Of note, HIV infection was associated with a significantly impaired IFN-g production of NK cells as compared to healthy controls with NK cells from HIV patients under HAART displaying the lowest activity (Figure 1B).

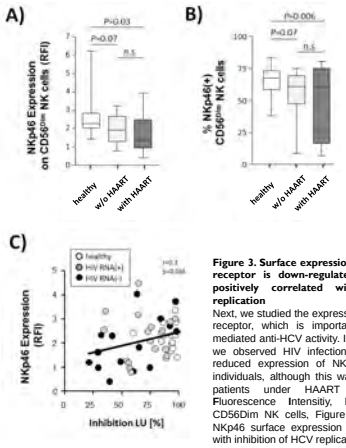


Figure 3. Surface expression of the activating NKp46 receptor is down-regulated in HIV infection and positively correlated with inhibition of HCV replication
Next, we studied the expression of the activating NKp46 receptor, which is importantly involved in NK cell-mediated anti-HCV activity. In line with previous reports, we observed HIV infection to be associated with a reduced expression of NKp46 compared to healthy individuals, although this was significantly only in HIV patients under HAART (NKp46 RFI, **R**elative **F**luorescence **I**ntensitiy, Figure 3A; % NKp46+ CD56Dim NK cells, Figure 3B). Moreover, we found NKp46 surface expression to be positively correlated with inhibition of HCV replication (Figure 3C).

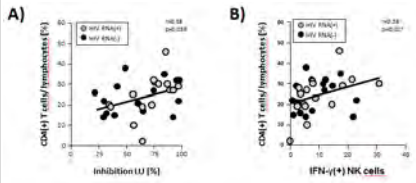


Figure 4. Frequency of CD4+ T lymphocytes was correlated with inhibition of HCV replication and IFN-g production of NK cells
CD4+ T cells have been shown to modulate NK cell activity. Accordingly, we observed frequency of CD4+ T lymphocytes to be significantly correlated with PBMC-mediated inhibition of HCV replication and IFN-g production of NK cells, respectively (Figure 4 A/B).

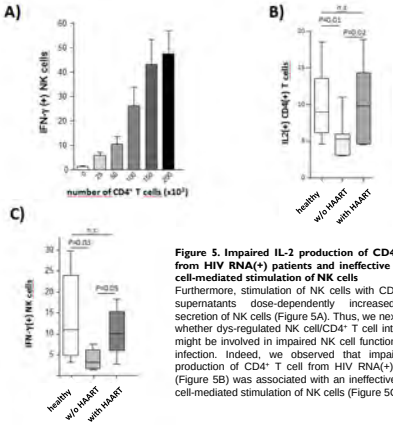


Figure 5. Impaired IL-2 production of CD4+ T cell from HIV RNA(+) patients and ineffective CD4+ T cell-mediated stimulation of NK cells
Furthermore, stimulation of NK cells with CD4+ T cell supernatants dose-dependently increased IFN-g secretion of NK cells (Figure 5A). Thus, we next studied whether dys-regulated NK cell/CD4+ T cell interactions might be involved in impaired NK cell functions in HIV infection. Indeed, we observed that impaired IL-2 production of CD4+ T cell from HIV RNA(+) patients (Figure 5B) was associated with an ineffective CD4+ T cell-mediated stimulation of NK cells (Figure 5C).