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Reduced expression of Blimp-1 on memory B cells in patients with HIV-1 infection suggests distinct roles of this molecule for B and T cell regulation.

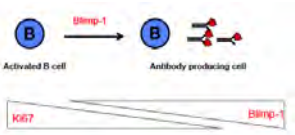
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Background

Blimp-1 has long been recognized as master regulator for B cell development and has additionally been recognized as important rheostat, balancing effector function and T cell exhaustion (1, 2). Although several studies described Blimp-1 in the context of T cell exhaustion in viral infections (3, 4, 5, 6), the role of Blimp-1 was first and primarily defined as a "master regulator" of terminal B cell development. Blimp-1 attenuates the expression of many transcription factors, thereby inhibiting B cell proliferation and B cell receptor mediated activation while promoting immunoglobulin secretion and plasma cell differentiation (1, 2).

Figure 1: Functional effects of different amounts of Blimp-1 and Ki67 expression in B cell differentiation.



Methods and Patients

Written informed consent was obtained from all patients and the study was approved by the local ethics committee. In a cohort of 26 individuals, classified as healthy donors (n = 7), treatment naïve HIV-1 infected patients (n = 9) and HIV-1 infected patients, who received combination antiretroviral therapy (cART) (n = 10).
Viral loads were below the limit of detection in all treated patients, mean viral load in the group of treatment naïve patients was 3 900 000 copies/mL (range: 54 – 13 000 000 copies /mL).
CD4 T cell count ranged from 4 to 690/µl (mean: 263/µl) in the group of treatment naïve patients versus 154 – 675/µl (mean: 590/µl) in the group of treated patients.
B cell memory subsets were defined as activated memory B cells (CD20+/CD21lo/CD27int), tissue like memory B cells (CD20+/CD21lo/CD27-), resting memory B cells (CD20+/CD21hi/CD27int) and naïve memory B cells (CD20+/CD21lo/CD27lo) as previously described (7).
Intracellular staining was performed using Blimp-1 antibody (Santa Cruz (C-21): sc-13206). All samples were run on an LSR II (BD) and analyzed with FlowJo 10.0.7.

Results

Figure 1: Representative fluorescence-activated cell sorter plot showing Blimp-1 and Ki67 expression on activated memory B cells ($CD20^+/CD21^{lo}/CD27^{int}$) in a HIV-1 seronegative (left) and a HIV-1 positive, treatment naïve individual (right).

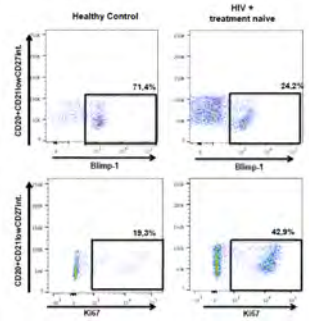


Figure 2: Blimp-1 expression is significantly downregulated in HIV-1 positive individuals compared to HIV-1 seronegative individuals. Treatment naïve patients showed an even lower expression of Blimp-1 than patients on cART (p = 0.0001; p = 0.008).

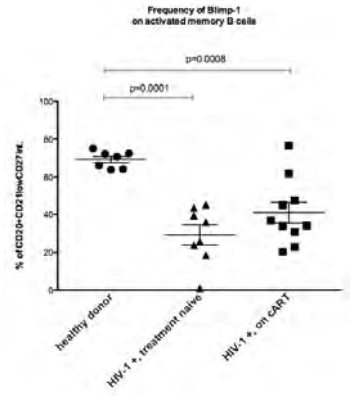


Figure 3: Ki67 expression is significantly upregulated in HIV-1 positive individuals compared to HIV-1 seronegative individuals. Treatment naïve patients showed an even higher expression Ki67 than patients on cART (p = 0.0021; p = 0.031).

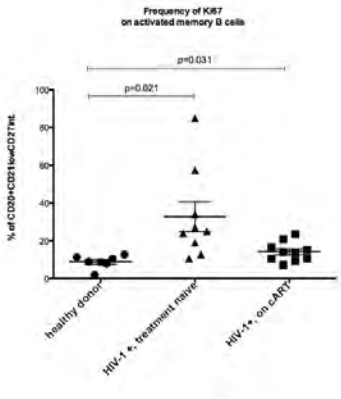
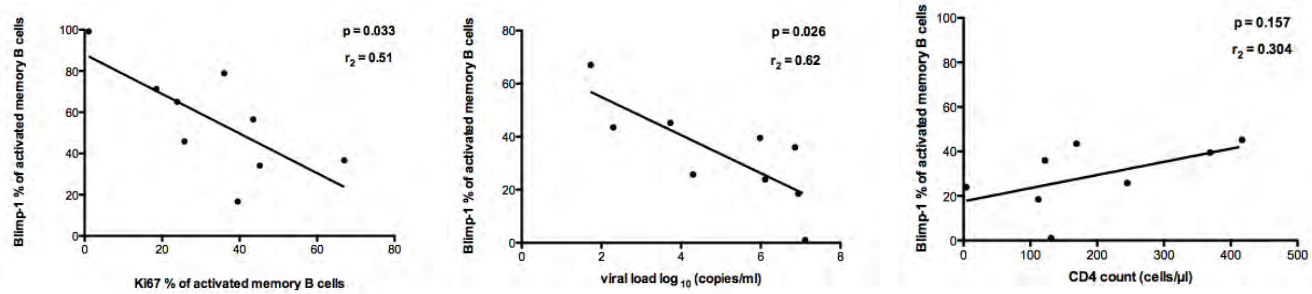


Figure 4: Expression of Blimp-1 correlated inversely with Ki67 expression (p = 0.033, r_2 = 0.51) and with HIV-1 viral load (p = 0.026, r_2 = 0.61). Blimp-1 expression did not significantly correlate with CD4+ T cell count (p = 0.157, r_2 = 0.304).



Conclusions

To our knowledge, this alteration of Blimp-1 expression on activated memory B cells in patients with HIV-1 infection, which is different from the corresponding expression pattern seen in T cells of HIV-1 infected patients has not been described before. We propose to further investigate the hypothesis whether down-regulation of Blimp-1 expression on activated memory B cells in patients with HIV-1 infection leads to uncontrolled differentiation into antibody secreting cells and consequently to an impaired production of neutralizing antibodies that has been described in HIV infection.
Further phenotypic and functional studies are required to confirm our preliminary results and to further investigate the controversial and seemingly complex role(s) of Blimp-1 in T as well as B cells in different HIV-1 infected subgroups, such as elite controllers and long-term nonprogressors.

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Acknowledgements

We thank the patients who participated in this study. This work was supported by the Deutsche Leberstiftung (CB), by the German Research Agency (JSzW, SFB841 project A6) and by the DZIF (German Center for Infection Research, JSzW, CB, JvL).