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Editorial Open Access

Importance of HLA Class I Amino Acid Position 194 and LILRB1 Receptor in HIV Disease Progression

Alba Grifoni[1] **and Massimo Amicosante**[1,2*]

[1]*ProxAgen Ltd, Sofia, Bulgaria*

[2]*Department of Biomedicine and Prevention, University of Rome "Tor Vergata", Rome, Italy*

[*]**Corresponding author:** Massimo Amicosante, Department of Biomedicine and Prevention, University of Rome "Tor Vergata", Rome, Italy, Tel: 390672596202; Fax: 390672596202; E-mail: amicosan@uniroma2.it

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Editorial

HIV-specific T-cell response, and in particular CTL, plays a key role in controlling HIV infection [1]. An increasing importance is currently recognised also to innate immune response, particularly the one associated to NK cells and the interaction of its receptor with HLA class I molecules [2]. We have recently performed an immunogenetic study in a defined cohort of children infected during a hospital outbreak with a monophyletic strain of HIV-1 [3], assessing the role of amino acid polymorphisms in HLA molecules [4,5].

As expected from previous immunogenetic studies [6,7], the large number of residues found associated with Long Term Non Progressor (LTNP) or progression to AIDS, have been located in the HLA-B locus, and more in general in the HLA molecule domains contributing to the formation of the antigenic peptide binding groove [4,5]. However, other amino acid residues resulted important for HIV progression outside the area of binding with the antigen peptide. Among them, the polymorphism Val 194 located on the α3-domain of HLA-B, resulted associated with LTNP [5].

Amino acid position 194 of HLA-B has been found to take part in the interaction with LILRB1 receptor (ILT2/LILRB1/CD85j) when occupied by Val [8-10]. Change in the strength of interaction between HLA-B molecules carrying Ile 194 and LILRB1 receptor might lead to rapid HIV progression. Although previous data suggest that the expression of LILRB1 receptor on the cell surface remains unchanged in subjects with different HIV progression, presences of different amino acids at the polymorphic position 194 of HLA-B might modify the interaction with LILRB1[11], influencing the strength of binding, as already reported about the LIR1-HLA-A interaction [12].

We extended this first evidence analyzing HLA-B alleles carrying Val/Ile 194 through immune-informatic approach to evaluate how this amino acid position could affect the interaction with different LILRB1 haplotypes. HLA-B alleles carrying Ile 194 polymorphism show a higher strength of interaction respect to HLA-B alleles carrying Val 194 for all the LILRB1 haplotypes analyzed, both in terms of general number of contacts and H-bonds evaluated in the site of interaction [13]. These results are in agreement with recent studies highlighting an influence of allelic variation and conformation of HLA class I on LILR binding particular in HIV context [10,12]. In addition, a stronger interaction of LILRB1.01 haplotypes with HLA-B alleles has been shown respect to LILRB1.02 and LILRB1.03 haplotypes, in agreement with the affinity constant observed between LILRB1 haplotypes and HLA-B*35:01 [14].

For the first time we propose a strong contribution of amino acid polymorphisms located in peptide binding pocket 1 able to modulate HLA-B/LILRB1 interaction [13]. This is consistent with previous results showing a different binding capability of LILRB1 with HLA-B*27:05 carrying different peptides [15].

In HIV infection expression of LILRB1 is increased respect to healthy donor. Higher is HIV viremia, higher is LILRB1 expression [11,16]. The evaluation of patients developing primary HIV-1 infection showed that a significant proportion of HIV-1 specific CD8 T cells express LILRB1 and the expression increase over the time in these cells [17]. LILRB1+ T cells response to HIV, CMV and EBV peptides was evaluated in HIV patients. Results show that in HIV patients LILRB1 is expressed in not terminally differentiated CTL instead of effector cells [18]. Moreover, the blockage of LILRB1/HLA interaction is able to increase IFNγ production [18], as well as it has been observed in NK cells suggesting that self HLA class I can regulate IFNγ production directly interacting with LILRB1.

Overall, immunogenetics and immune-informatics analyses on HLA/LILRB1 interaction show a contribution to HIV immune response with a key role for the polymorphism at position 194 that might be useful to predict HIV disease progression.

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