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Multiple immunogenetic aspects in susceptibility to HIV-1 infection progression toward AIDS and rational vaccine design

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Viral and host factors can influence HIV-1 progression, hence the definition of relevant parameters to be considered in the rational design of HIV vaccine relies on multiple aspects of host-pathogen interaction. However, the understanding of the functional contribution of immune-related genes in controlling HIV progression toward AIDS is limited by multiple issues, including the (i) genetic background due to individuals coming from different or large geographic area and (ii) viral strain variability in the evaluated cohort. We have analysed the contribution of multiple immune related factors in a cohort of children infected with a monophyletic strain of HIV-1 (CRF02_AG) during an outbreak in the Benghazi Children Hospital in Libya, minimizing the above issues. Among the HLA factors associated with progression to AIDS, HLA-B locus was the most interesting locus presenting 10 positions located in peptide binding pocket B and F associated with long term non progressors (LTNP) or fast progressors (FP) in HIV-infected subjects. Polymorphic residues 11S, 74D and 94T, were associated with AIDS progression; while amino acid residues 66N, 80I, 81A, 82L and 83R, were associated with non-progression. From a functional point of view of HLA molecules, the found association correlated with the number of epitopes recognized *in silico* by the combination of the HLA alleles along the HIV-1 protein sequences circulating in the cohort, and the capability of in vitro response. An increasing importance is currently given to the innate immune response, particularly the one associated to NK cells and the interaction of its receptor with HLA class I molecules. In this context, homozygosis of epitope Bw4 in HLA-B has been associated with delayed progression (Bw4/Bw4: LTNP=30.8%, FP=8.7%, $p<0.0019$). In addition, for the first time, the polymorphism Val194 located in the α3-domain of HLA-B, showed an association with LTNP (LTNP=73.08%, FP=34.78%; $P<0.02$). When Val is present at position 194, HLA-B is known to interact with the receptor LIR1 (ILT2/LILRB1/CD85j). Gene variants associated in alteration of the humoral immune response were associated with HIV-progression. In particular, the polymorphisms of enhancer HS1,2, member of the 3' regulatory region of the Ig heavy chain cluster is known to play a role in the variation of the humoral response leading to pathological conditions. All these results suggest that the progression to AIDS might be determined by the combination of different immunogenetic factors, in part determined by the peptide binding capability to HLA molecules and in part by the interaction between HLA class I molecules and NK's receptors. Improved knowledge of HLA peptide presentation and recognition in the context of canonical and non-canonical receptors may allow the development of new strategies for manipulating the immune response against HIV.

Biography

Massimo Amicosante, graduated at the University "La Sapienza" in 1991, he is currently assistant professor at the University of Rome "Tor Vergata". He has a long track record in immunogenetics and immunology of infectious diseases as well as in developing immuno-informatics models applied to infectious diseases susceptibility, with particular applications to antigen recognition and the use of peptides and proteins for diagnosis and vaccine development. He has considerable experience in transfer technologies and has participated in support actions to the HIV-infected pediatric cohort of the Benghazi Children Hospital (Libya) outbreak.

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