Project : Effect of HLA-B dimorphism on NK cell mediated immunity during chronic viral infections

Funding from the Association of Physicians of Great Britain and Ireland supported consumable costs /research staff salary to explore the effects of HLA-B dimorphism on Natural Killer (NK) cells mediated immunity against HIV-1 infection. We investigated the effect of this polymorphism on the phenotype and functional capacity of peripheral blood NK cells in a cohort of thirty-six African individuals with human immunodeficiency virus type 1 (HIV-1)/HCMV co-infection.

Summary of findings: HLA-E acts as powerful modulator of the immune response, serving as a ligand for NKG2 receptors that provide a functionally complementary axis to the polymorphic KIR system for control of innate lymphocyte subsets. HLA-E binds signal peptides derived from the leader sequence of HLA-A, B, C and G proteins in order to achieve stable expression at the cell surface. -21M, the residue present in all HLA-A and -C and a minority of -B allotypes, facilitates folding and expression of HLA-E by providing a strong anchor residue in contrast to -21T, the residue present in the majority of HLA-B allotypes. This genetic segregation depending on HLA-B dimorphism leads to a binary form of NK cell education and functional responsiveness in HCMV seronegative donors of European origin by either supplying NKG2A or KIR ligands. A similar effect was not seen in an African cohort with HIV/HCMV co-infection, where genetic and environmental factors could influence the NK cell repertoire and effector function. The presence of African specific alleles, together with alterations in the HLA-E peptide repertoire due to the availability of peptides derived from other cellular and viral sources that could arise during HIV/HCMV coinfection, trigger the expansion of adaptive NK cells expressing the activating receptor NKG2C with subsequent functional consequences. The lack of -21M expression could thus become redundant in HCMV seropositive individuals where UL40 or HLA-G derived peptides may stabilise the expression of HLA-E and fine tune NK cell activation and antibody driven adaptive responses. Increased efforts to understand how NK cells are functionally calibrated to self-HLA during chronic viral infections will pave the way to developing targeted therapeutic interventions to overcome the current barriers to enhancing immune-based antiviral control.

Future work: Future larger studies aimed at dissecting the effect of different HLA-E/peptide ligands on adaptive NK cells in relation to -21 HLA-B polymorphism, during disease are required, in order to facilitate realisation of the translational potential of specific NK cell subpopulations and exploit the NKG2C/HLA-E axis to enhance NK cell functionality. We are planning to extend these findings in larger HIV infected cohorts but also other chronic viral infections such as HBV. This work has initiated new collaborations and laid strong foundations for future funding applications from external sources to support ongoing work.

The findings of our work have been accepted for publication *Frontiers in Immunology* (in press) and AoP has been acknowledged as a funder.

Subordinate effect of -21M HLA-B dimorphism on NK cell repertoire diversity and function in HIV-1 infected individuals of African origin

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