Retrovirology

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Oral presentation

Human and chicken antibodies to CCR5-ECL1 block mucosal and systemic HIV infection

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Background

The HIV-1 coreceptor CCR5 and antibodies against it are relevant for HIV-1 vaccine design and therapy. Antibodies to the first loop (ECL1) of CCR5 have been identified in HIV-exposed uninfected individuals (ESN) and in HIV-positive non-progressing subjects. To better define the role of anti CCR5 antibodies in blocking HIV infection, we characterized their role at mucosal level and we defined the fine epitope mapping. Moreover, we tried to induce and reproduce this CCR5 specific immune response in animal model, such as mouse and chicken.

Materials and methods

PBMC, CCR5 transfected cell line and epithelial cells were used to evaluate HIV blocking activity by CCR5 specific IgA and IgG. A two chambers system was established to model HIV-1 infection across the human mucosal epithelium. Moreover, to better define the region recognized by CCR5-antibodies, a panel of synthetic peptides spanning the CCR5-loop1 region, displaying Glycine or Alanine substitutions, was assayed for antibody binding with anti-CCR5 antibodies from ESN. The mutagenized region of CCR5 was then used to immunize mice and chicken.

Results

Either serum or mucosal IgA to CCR5 were able to specifically block transcytosis of CCR5- but not CXCR4-strains across a tight epithelial cell layer by interacting with the first extracellular loop of the receptor (aa:YAAAQWDFGNTMCQ). Noteworthy, antibodies against other regions of CCR5 had no effect on HIV mediated transcytosis. Aminoacidic substitutions in positions Ala95 and Ala96 (A95-A96) were found to increase antibody-peptide binding in comparison with wild-type peptide (Phe95-Asp96). Ala95-96 peptide was shown to induce mouse and chicken antibodies displaying biological activity at very low concentrations (ng/ml). Strikingly, chicken antibodies to Ala95-96 specifically recognize human CCR5 molecules, downregulate receptor from lymphocytes, inhibit CCR5-dependent chemotaxis and prevent infection of several R5-viruses. Structural characterization by NMR spectroscopy proved the high flexiblility of isolated epitopes and suggested that Ala95-96 substitutions determine a slightly higher tendency to generate helical conformations combined with a lower steric hindrance of the side chains in the peptides.

Conclusion

These findings may be relevant to understand the way to induce strong and efficient HIV blocking antibodies able to protect from infection at mucosal site. Moreover, the chicken model proves a simple and inexpensive approach that could be translated into clinical practice.