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Oral presentation

Bile-salt stimulated lipase in human milk binds DC-SIGN and inhibits HIV-1 transmission

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Background

Approximately 20% of HIV-1 infected breastfeeding mothers transmit virus to their infants. It has been hypothesized that dendritic cells expressing C-type lectins, such as DC-SIGN, play an important role in the establishment of infection with HIV-1 and several other pathogens.

Within our laboratory we have identified that Bile Salt Stimulated Lipase (BSSL) is able to bind to DC-SIGN and block HIV-1 transmission via dendritic cells. The C-terminal part of BSSL contains a highly polymorphic repeat section coded by exon 11 of the gene and is composed of an array of 11 amino acid repeats.

Materials and methods

We have studied a large number of human milk samples from HIV-1 negative mothers. The BSSL protein was analyzed by size fractionation and iso-electric focusing. We studied the genomic structure of the gene through PCR amplification and sequencing of the BSSL repeats for a group of selected mothers.

Results

Milk samples from a large number of different mothers (n=25) were identified that demonstrated variant levels of inhibition to viral transfer. We have studied specific BSSL genotypic as well as phenotypic properties in order to identify what provides for the large variation of milk binding DC-SIGN. The tested milk samples were divided into weak binding and strong binding groups based on their DC-SIGN binding capacity. When comparing the PCR results for the BSSL repeat number we identified a link between the number of repeat domains and inhibition, with the more repeats binding less efficiently. A selection of weak and strong binders with identical repeat numbers was also made. Sequencing of this selected group revealed a mutation in the repeat section of an extreme weak binder on an interesting position with regards to BSSL glycosylation. Further analysis at the proteomic level was performed with a higher molecular mass for BSSL in the weak binding group being identified. Analysis of the DIGE results showed a shift in pI of BSSL in the weak binding group for 3 out of 5 cases.

Conclusions

Our results demonstrate that multiple factors contribute to the differential binding of human milk to DC-SIGN. Variation in the DC-SIGN binding capacities of BSSL may provide for alterations in transmission patterns of pathogens or in altering the immune mediated responses mounted in children against milk-borne pathogens. Furthermore, understanding these differences in BSSL could aide in the development of new agents aimed at preventing pathogen transmission across a mucosal barrier.