LACTOFERRIN-DERIVED PEPTIDES WITH ANTI- HEPATITIS B VIRUS ACTIVITY- *IN VITRO* STUDIES

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Lactoferrin (Lf) is an iron binding glycoprotein which was shown to exhibit antiviral activity at an early phase of infection. It was suggested that Lf interaction with host cell surface molecules such as glycosaminoglycans (GAGs) could be part of the mechanism of action. Two GAGs binding sites located in the N-terminal (N-t) region of Lf could be involved in its antiviral activity, one of them being a cationic cluster (GRRRR).
We have investigated seven human Lf (HLf)-derived peptides (HLP), corresponding to the N-t domain of the native protein (1-47 amino acids sequence) for their capacity to prevent hepatitis B virus (HBV) infection and replication using HepaRG and HepG2.2.2.15 cell lines. Of the series tested, four peptides demonstrated inhibition of HBV infection in HepaRG cells between 40 to 80%. The most potent inhibitor was HLP_{1-23}, a peptide containing the GRRRR cluster which prevented HBV infection at 250 µM by neutralizing the viral particles. In an effort to improve the antiviral activity of HLP_{1-23} we further used computer modeling followed by chemical synthesis. A new mutant peptide with increased overall positive charge and aromaticity, supposedly displaying improved affinity through additional GAGs binding site and increased stability through supplementary aromatic stacking interactions was designed. The new peptide HLP_{1-33} was assayed for potential cytotoxicity in HepaRG cells and anti-HBV activity on HepaRG cell system. The results revealed that HLP_{1-33} peptide has good solubility in aqueous solution and is not toxic for concentrations up to 100 µM. Preliminary results showed that HLP_{1-33} is able to inhibit HBV infection on HepaRG cells by 50% at 100 µM. Inhibition of HBV replication in HepG2.2.2.15 cellular systems is currently under investigation.
Lf-derived peptides may constitute a non-toxic approach for potential clinical therapy in inhibiting early steps of HBV infection or protection of regenerated hepatocytes from *de novo* infection.

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