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SO4-05 OA. The intracellular production of HIV antigenic peptides is guided by predictable motifs and can be altered: implications for immunogen design

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Background

The success of a T cell-based vaccine relies not only on the identification of protective epitopes but also on the capacity of vaccinated tissues to produce and present these epitopes to immune cells. Defining predictable events leading to efficient epitope presentation is critical to immunogen design. Epitopes are short protein fragments escaping degradation, but factors controlling the efficiency of epitope production are unknown. We previously identified portable flanking sequences altering epitope production and antigenicity. In order to define motifs driving efficient epitope production, we analyzed the degradation of long HIV peptides into shorter fragments as well as the capacity of antigenic peptides to sustain intracellular degradation.

Methods

We combined epitope processing assays with computational analysis of degradation products. Long HIV peptides were incubated with PBMC extracts and degradation fragments were identified by mass spectrometry. Additionally we measured the intracellular stability of 167 HIV epitopes by HPLC profile analysis, where the surface of the peak corresponding to one peptide is proportional to the epitope amount. We performed a computational analysis of peptides resistant or sensitive to degradation. Finally we introduced stability or degradation motifs in peptides and measured the stability of mutated sequences.

Results

The analysis of hundreds of degradation fragments identified 36 motifs enriched in fragments and absent in cleavage sites. We also demonstrate a great heterogeneity in intracellular epitope stability (half-lives: 210 ms–39 min). We identified 14 motifs associated with intracellular stability and 21 with rapid degradation of epitopes. Introducing stability motifs into unstable peptides increased stability by 9-fold whereas mutating these motifs in stable peptides decreased stability by up to 100-fold.

Conclusion

This is the first definition of rules driving the production of antigenic peptides. These data suggest that epitope processing from HIV immunogens could be manipulated so as to enhance production of protective epitopes and increase intracellular degradation of non-protective epitopes.