

Rapid evaluation of diverse chemical transformations on bacteriophage- displayed peptides

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Chemically modified genetically encoded peptide libraries encompass broader chemical space that enables rapid discovery of proteolytically resistant and potent drug leads. However, evaluating chemical modifications on phage-displayed peptide remains challenging due to their ultra-low concentrations. Despite extensive efforts to assess these modifications—such as using ESI-MS for identifying modifications of phage-displayed peptides or using MALDI-TOF-MS to detect chemical transformations on p8-displayed peptides—current methods are often time-consuming or impractical for certain applications, hindering the development of new modification strategies for generating chemically modified peptide libraries in drug discovery. Herein, we propose a strategy that enables rapid display of peptides regards of sequence and size on phage and offer convenient kinetic evaluation of chemical transformation on phage-displayed peptide. In this work, DBCO was installed on p8 proteins of M13 phage, followed by “click” chemistry attachment of chemically synthesized azido peptides. Subsequently, the kinetics of diverse chemical transformations on phage-displayed peptide were evaluated using MALDI-TOF-MS, highlighting the extreme convenience and rapidity of this method. All modification, detection, and purification (if needed) steps can be performed in parallel, with the potential for fully automation, significantly advancing the development of new chemical modification strategies of peptide libraries.