PARADISE REGAINED:

Deciphering Immunogen Code via Transglutaminase Modification Motif for Elixir Design

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Related Patent Applications

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Abstract

Previously we found transglutaminase modification motifs correspond to immunodominant epitope sequences of a protein in antigen processing. In this study we suggest the presence of acidic D/E residue 3-mer before and 8-mer after the glutamine (Q) residue as a key criterion to determine immunodominant epitopes in a protein. With this principle, we characterized the epitope sequences in lamin A/C, synuclein, type I and II collagens, fibronectin, p53, BRCAs, steroidogenic factor 1, DDX4, and GP120 for the design of elixir immunogen products.

We found Q109 as the primary transglutaminase modification site in synuclein (PCT/IB2022/000547). There we figured out that the glutamine and its follow-up 5 residues on the C terminal of a protein compose a minimal determinant motif for transglutaminase modification and, more importantly, the transglutaminase modification motifs determined by our platform could finally correspond to the substrate's immunodominant epitope sequences in antigen processing. In this study, we further suggest the epitope variants could compass up to 3 residues before the glutamine (Q) on the N terminal and 8 residues after on the C terminal, where the acidic residue D or E plays a crucial role in which its negative charged side chain may greatly facilitate Q motif's interaction with the positive charged lysine (K) substrate. Moreover, the minimal determinant motif usually follows a pattern of D/E plus hydrophobic linker plus D/E, though sometimes only one group of D/E is necessary.

This principle first embodies in synuclein epitope GAPQEGILEDMP which includes a hydrophobic cap GAP before Q and a typical D/E plus hydrophobic linker plus D/E after the Q. A similar pattern applies to fibronectin epitope APFQDTSEYIIS. But in HIV GP120 epitope PNPQEVVLVNVT the minimal determinant motif shows a D/E plus hydrophobic tail pattern. The p53 epitope DIEQWFTEDPGP composes a D/E cap and a minimal determinant motif with a hydrophobic linker plus D/E pattern. The lamin A/C epitopes DEYQELLDIKLA and EDLQELNDRLAV present a D/E cap and a minimal determinant motif of D/E plus hydrophobic linker plus D/E. So do COL1A1 epitope GAPDQEFGFDVGP and COL2A1 epitope GGPEQEFGVDIGP. We also deduce the immunogen peptides VTGQEVELTTVA and MADQTFISIVDW from the protein steroidogenic factor 1 for the maintenance of sex hormone-producing cells in both male and female, KELQEPECIIVA from ddx4 for better germ cells, and

DYGTQESISLLEV from BRCA1 and RALQDGAELYEA from BRCA2 for the prevention of breast, prostate and other oncogenic mutations.