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Novel mutant P277 peptide VP to ameliorate atherogenic side-effects and to preserve anti-diabetic effects in NOD mice

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Abstract

P277 is a 24 amino-acids peptide, residues 437 to 460 of human heat shock protein 60 (HSP60). P277 or sequence repeated 6×P277 was previously found showing potency preventive and therapeutic anti-diabetes functions in NOD mice, but aroused atherosclerosis due to the induction of anti-HSP65 autoantibodies as reported. To determine the intrinsic B epitope sequence, we screened P277 with pepscan method and then proved by detection of sera IgG from peptide fragments vaccinated mouse and rabbits. Results indicated HSP60 443-448 (ALLRCI) is potential intrinsic B epitope sequence of P277. We modified P277 by deleting the former three amino acids of ALLRCI (VP) or replacing these six with alanine (AP). The detection of serum lipid parameter in NOD mice and aorta endothelial damage levels in high-cholesterol diets fed rabbits demonstrated that VP induced higher anti-diabetes efficacy and caused less arteriosclerosis-liked diseases separately. With less TLR2/4 activation of dendritic cells and macrophages, VP treatment reduced Th1 related P277 specific pro-inflammatory cytokines production and increased regulatory immune responses both in vivo and in vitro. These results indicated that optimized VP peptide might serve as a promising candidate for mouse type 1 diabetes therapy.