"*Novel Peptide-based Protein Arginine Deiminase IV Inhibitor for suppression of Autoimmune Disease*"

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Peptidyl arginine deiminase 4 (PAD4) plays a vital role in the posttranslational modification of protein known as citrullination. PAD4 catalyses the citrullination process by converting arginine to citrulline, resulting in the citrullinated protein which is rendered as autoantigen in autoimmune diseases, for example, multiple sclerosis and rheumatoid arthritis (RA). Therefore, PAD4 has emerged as a potential therapeutic target for autoimmune diseases especially RA. Antithrombin is one of the natural substrates of PAD4. Peptide inhibitors with different lengths and sequences were designed based on the ten citrullination sites in antithrombin. In total, 90 peptides were designed and docked with PAD4 using HADDOCK. Peptides with HADDOCK score lower than -90 were selected for modification by substituting the target residue, arginine, to its analogue, lysine. Forty-two modified peptides were again docked against PAD4 and based on the docking results, top peptides which fit well in the enzyme binding site were selected for further investigation. As a result, six potential peptide inhibitors, namely KE11, KK11, KL11, KD9, WK9 and KN7, were selected and synthesised for *in vitro* activity study. *In vitro* enzyme inhibition assay showed that KE11, KL11 and KN7 reduced the PAD4 activity. However, the IC_{50} values of all three selected peptides were more than 2mM. This showed that the peptides are relatively weak as PAD4 inhibitors. Secondary structure study shows that the free peptides are having unordered structure. Molecular docking results shows that the peptides have similar binding modes and interaction with PAD4 in which a bent conformation is induced on the peptides upon binding to the enzyme. The peptides interact with some of the important residues in the active site, such as Cys645, Asp350 and Asp473. In conclusion, although the designed peptides displayed rather high IC_{50} values against PAD4, the peptides do interact with the essential amino acids in the binding pocket, so the peptides derived from antithrombin could be further modified in future to improve the inhibition ability.

Funded by Toray Science Foundation, Japan

Presented at the MTSF Grant Research Symposium held on 26 November 2019.