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[Keynote Talk]: Bioactive Cyclic Dipeptides of Microbial Origin in Discovery of Cytokine Inhibitors

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Abstract : Cyclic dipeptides are simple diketopiperazine derivatives being investigated by several scientists for their biological effects which include anticancer, antimicrobial, haematological, anticonvulsant, immunomodulatory effect, etc. They are potentially active microbial metabolites having been synthesized too, for developing into drug candidates. Cultures of Pseudomonas species have earlier been reported to produce cyclic dipeptides, helping in quorum sensing signals and bacterial–host colonization phenomena during infections, causing cell anti-proliferation and immunosuppression. Fluorescing Pseudomonas species have been identified to secrete lipid derivatives, peptides, pyrroles, phenazines, indoles, aminoacids, pterines, pseudomonic acids and some antibiotics. In the present work, results of investigation on the cyclic dipeptide metabolites secreted by the culture broth of Pseudomonas species as potent pro-inflammatory cytokine inhibitors are discussed. The bacterial strain was isolated from the rhizospheric soil of groundnut crop and identified as Pseudomonas aeruginosa by 16S rDNA sequence (GenBank Accession No. KT625586). Culture broth of this strain was prepared by inoculating into King's B broth and incubating at 30 ºC for 7 days. The ethyl acetate extract of culture broth was prepared and lyophilized to get a dry residue (EEPA). Lipopolysaccharide (LPS)-induced ELISA assay proved the inhibition of tumor necrosis factor-alpha (TNF-α) secretion in culture supernatant of RAW 264.7 cells by EEPA (IC50 38.8 µg/mL). The effect of oral administration of EEPA on plasma TNF-α level in rats was tested by ELISA kit. The LPS mediated plasma TNF-α level was reduced to 45% with 125 mg/kg dose of EEPA. Isolation of the chemical constituents of EEPA through column chromatography yielded ten cyclic dipeptides, which were characterized using nuclear magnetic resonance and mass spectroscopic techniques. These cyclic dipeptides are biosynthesized in microorganisms by multifunctional assembly of non-ribosomal peptide synthases and cyclic dipeptide synthase. Cyclo (Gly-L-Pro) was found to be more potentially (IC50 value 4.5 µg/mL) inhibiting TNF-α production followed by cyclo (trans-4-hydroxy-L-Pro-L-Phe) (IC50 value 14.2 µg/mL) and the effect was equal to that of standard immunosuppressant drug, prednisolone. Further, the effect was analyzed by determining mRNA expression of TNF-α in LPS-stimulated RAW 264.7 macrophages using quantitative real-time reverse transcription polymerase chain reaction. EEPA and isolated cyclic dipeptides demonstrated diminution of TNF-α mRNA expression levels in a dose-dependent manner under the tested conditions. Also, they were found to control the expression of other pro-inflammatory cytokines like IL-1β and IL-6, when tested through their mRNA expression levels in LPS-stimulated RAW 264.7 macrophages under LPS-stimulated conditions. In addition, significant inhibition effect was found on Nitric oxide production. Further all the compounds exhibited weak toxicity to LPS-induced RAW 264.7 cells. Thus the outcome of the study disclosed the effectiveness of EEPA and the isolated cyclic dipeptides in down-regulating key cytokines involved in pathophysiology of autoimmune diseases.In another study led by the investigators, microbial cyclic dipeptides were found to exhibit excellent antimicrobial effect against Fusarium moniliforme which is an important causative agent of Sorghum grain mold disease. Thus, cyclic dipeptides are emerging small molecular drug candidates for various autoimmune diseases.

Keywords : cyclic dipeptides, cytokines, Fusarium moniliforme, Pseudomonas, TNF-alpha
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