Lipidated alpha-Peptide/beta-Peptoid Hybrids with Potent Antiinflammatory Activity - DTU Orbit (10/02/2019)

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In this study, we investigated, optimized, and characterized a novel subclass of host defense peptide (HDP) mimics based on a-peptide/beta-peptoid hybrid oligomers with an alternating cationic/hydrophobic design with respect to their ability to modulate the pro-inflammatory response by human primary leukocytes upon exposure to bacterial components. Structure-activity studies revealed that certain lipidated a-peptide/beta-peptoid hybrid oligomers possess anti-inflammatory activities in the submicromolar range with low cytotoxicity, and that the anti-inflammatory activity of the HDP mimics is dependent on the length and position of the lipid element(s). The resulting lead compound, Pam-(Lys-beta NSpe)(6)-NH2, blocks LPS-induced cytokine secretion with a potency comparable to that of polymyxin B. The mode of action of this HDP mimic appears not to involve direct LPS interaction since it, in contrast to polymyxin B, displayed only minor activity in the Limulus amebocyte lysate assay. Flow cytometry data showed specific interaction of a fluorophore-labeled lipidated a-peptide/beta-peptoid hybrid with monocytes and granulocytes indicating a cellular target expressed by these leukocyte subsets.