141f Effect of the Hydrophobic Helix Length and Side Chain Chemistry on Biomimicry in Peptoid Analogues of Lung Surfactant Protein C

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The hydrophobic proteins of lung surfactant (LS), SP-B and SP-C, have been shown to be of great importance for the dynamic behavior of LS. Their inclusion in animal-based surfactant replacement therapies (SRTs) for the treatment of nRDS has been demonstrated to be more clinically effective than synthetic surfactant preparations, which lack the hydrophobic proteins. However, due to concerns with animal-derived surfactants, recent investigation has focused on the creation of synthetic mimics of LS proteins in order to create a fully synthetic SRT with the same efficacy of natural LS. One interesting approach is the use of poly-*N*-substituted glycines, or "peptoids" for this objective. Peptoids have close structural similarity to peptides, form stable helices, resist protease degradation, and are less prone to immune system recognition than peptides. These properties make peptoids an excellent candidate for the mimicry of natural molecules that rely on helical structure for proper bioactivity such as the hydrophobic proteins of LS.

In order to develop a non-natural, bioactive mimic of SP-C, we have synthesized, purified, and performed in vitro testing of length-dependant series of two classes of mimics: those utilizing α-chiral, aromatic side chains (*N*spe) in the helical region and those utilizing α-chiral, aliphatic side chains (*N*ssb) in helical region. Both classes of mimics were designed to capture the amphipathic patterning and highly helical nature of a truncated, non-palmitoylated peptide version of SP-C, which has been shown to have activities similar to the full-length lipopeptide. These mimics were studied in order to gain greater insight into whether the helical stability or the ability to more closely mimic the aliphatic side chains of the hydrophobic region of SP-C has a greater impact on its surface activity in a lipid environment. In addition to side chain chemistry, the specific length of the hydrophobic, helical region of both classes of mimics was also investigated by varying the number of α-chiral, helix forming peptoid monomers in this region.

Circular dichroism spectroscopy gives evidence that both classes of peptoid-based SP-C mimics form stable, helical structures in solution. Pulsating bubble surfactometry, Langmuir-Wilhelmy surface balance, and fluorescence microscopy experiments provide evidence that the surface activities and film morphologies of the peptoid-based SP-C mimics are tolerant to changes in the helical side chain chemistry with slight differences in surface activities associated with sequence length. These results are promising for the development of a synthetic, biomimetic, peptoid-based LS formulation.