Ultrashort Peptides as Bifunctional Nanomaterials

Biomaterials have contributed greatly to advances in modern medicine enhancing patients’ quality of life however they are regarded as foreign objects by the human body [1]. Their presence and sometimes trauma caused by insertion of a biomaterial triggers host inflammatory mediators. They also provide an ideal surface for bacterial attachment and biofilm formation. These can compromise biomaterial function and mechanical properties resulting in its failure or destruction of with associated negative effects on the patient and their outcomes [2].

Self-assembling ultrashort cationic peptides are an innovative form of antimicrobial hydrogels. Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used to treat pain and inflammation despite their systemic side effects. A combination of these may create a novel self-assembling biomaterial with dual properties— a localized antimicrobial action and ability to dampen the host immune response [3].

Gelation can be tailored to occur in response to physiological infective indicators: pH, Enzymes, Temperature

Thickening agents allow self-assembling properties with the site of infection [4]. This work focuses on the development of dual acting anti-inflammatory and antimicrobial self-assembling peptides with the incorporation of clinically used NSAIDs into our previously investigated self-assembling antimicrobial peptides with -FFKK.

Fig.1. Chemical structures of the NSAIDs conjugated to the synthesized peptides A) naproxen, B) ibuprofen, C) indomethacin

The ability to self-assemble to form hydrogels is determined by the primary peptide structure. Naproxen and indomethacin conjugates formed self-supporting hydrogels. Ibuprofen conjugates due to insufficient G' being one order of magnitude higher than G'' for all concentrations of peptides. FTIR further confirmed assembly with shoulders in the amide I region (1570 cm⁻¹) and characteristic peaks representative of β-sheet formation (1625 cm⁻¹) in an antiparallel arrangement (1675 cm⁻¹). Higher ordered nanofibrous assemblies were observed under cryo-SEM and TEM.

The hydrogels proved to be relatively non-hemolytic and non-toxic in vitro. Strong antibiofilm activity was demonstrated by all hydrogels. The optimal reduction in percentage viable biofilm was exhibited by IndFFKK against Staphylococcus aureus. The anti-inflammatory activity of the NSAIDs was not inhibited following coupling to the peptide with hydrogels showing inhibitory activity against both COX-1 and -2 enzymes.

Fig.2. Frequency sweep and rheological properties for NSAID conjugates at 2% (w/v). G' = storage modulus, G'' = loss modulus

Fig.3. FTIR spectra for the NSAID conjugates at 2% (w/v).

The antimicrobial properties of each concentration of peptide hydrogel were determined by the ability to reduce viable 24 hour biofilms of both Gram-positive (Staphylococcus aureus and Staphylococcus epidermidis) and Gram-negative bacteria (Escherichia coli and Pseudomonas aeruginosa)

Conclusions

This investigation has shown that self-assembled NSAID conjugated peptide hydrogels may have potential clinically. Dual activity means that such molecules could act as novel candidates for wound dressings and medical device coatings. Further to this, pH triggered assembly and cytotoxic investigations conducted thus far indicates the potential for targeted activity at the necessary site of action. The next step will be to character further the biocompatibility and enzymatic stability of these molecules.

References