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Dual Amino Acid Swap in MUC7-Derived Peptide Enhances Resistance and Modulates Zn(II) and Cu(II) Complex Stability, Secondary Structure and Antimicrobial Activity

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Streszczenie

Metal ion complexes with antimicrobial peptides are emerging as promising therapeutic agents, but their efficacy is often limited by rapid proteolytic degradation and poorly understood metaldriven mechanisms. Here, we stabilize a sequence derived from mucin 7 by introducing two D-amino acids at the site most susceptible to proteolytic cleavage and show that this subtle modification rewires its copper(II) and zinc(II) coordination chemistry and antimicrobial activity. The coordination, structure and activity of the modified peptide (peptidomimetic) with Cu(II) and Zn(II) were probed by potentiometry, mass spectrometry, multiple spectroscopies and quantum-chemical calculations, together with antimicrobial and antibiofilm assays. The peptidomimetic is resistant to enzymatic cleavage and forms thermodynamically more stable Cu(II) complexes with {3Nim} donor sets, in contrast to the native peptide which favors {2Nim} binding, while Zn(II) speciation is only modestly affected. Metal loading together with the D-amino-acid-induced increase in conformational flexibility converts the otherwise inactive peptide into a selective, metal-dependent antimicrobial peptide (AMP) that targets Streptococcus mutans and Streptococcus sanguinis, inhibits their biofilm formation at subinhibitory minimum inhibitory concentration (sub-MIC) levels and remains nontoxic to human fibroblasts. These results demonstrate how fine-tuning histidine-rich coordination environments by minimal stereochemical editing can be used to design stable, Cu(II)- and Zn(II)-based antimicrobial peptidomimetics with distinct, metal-specific mechanisms of action.

Słowa kluczowe

Antimicrobial activity, Equilibrium constant, Ions, Peptides and proteins, Peptidomimetics

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