

Metal-tuned antimicrobial peptides and zincophore pathways: from coordination chemistry to targeted therapeutics

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Escalating resistance among bacterial and fungal pathogens calls for new therapeutic strategies that go beyond classical small-molecule antibiotics. Antimicrobial peptides (AMPs) are attractive candidates because they can act through multiple mechanisms and often evade conventional resistance pathways. Biologically essential metal ions such as Zn(II) and Cu(II) further expand this chemical space: metal binding can modulate peptide structure, morphology, local charge and transport, thereby generating metallo-AMPs with distinct modes of action.

In this review, we discuss selected Zn(II)- and Cu(II)-binding AMPs and peptidic zincophores in which the link between coordination chemistry and biological activity has been analysed in detail. Rather than simply listing examples, we use these systems to show how a coherent research programme in bioinorganic AMP chemistry can be built around one guiding idea: connecting metal coordination to function across different peptide families. Pramlintide and shepherdins illustrate Zn(II)-driven conformational change and fibril formation associated with antifungal activity. Semenogelins and calcitermin highlight how histidine-rich motifs and local charge tuning can activate peptides without relying on nutritional immunity. Clavanins reveal a “chemical butterfly effect”, where subtle differences in pre-organization translate into changes in complex lability and antimicrobial outcome. Histatin systems show that metal-dependent effects can be strongly pH-gated. Finally, thermodynamic and structural studies of fungal zincophores and bacterial periplasmic transporters provide a basis for targeted peptide designs that exploit Zn(II) uptake pathways. Together, these case studies outline mechanism-based design principles for future metal-peptide therapeutics.

Słowa kluczowe

Metal-antimicrobial peptide complexes, Zn(II) and Cu(II) coordination, Structure–activity relationship, Bioinorganic mechanisms

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