From speciation to action: Cu(II) and Zn(II) tune histatins, but pH and enamel drive efficacy

Autorzy

Emilia Dzień

Aleksandra Mikołajczyk-Tarnawa

Agnieszka Matera-Witkiewicz

Krzysztof Szewczyk

Miquel Barceló-Oliver

Lilla Pawlik-Sobecka

Joanna Wątły

Magdalena Rowińska-Żyrek

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Histatins are histidine-rich salivary peptides whose antimicrobial activity emerges from a delicate interplay between proteolytic cleavage and metal coordination. We quantified Cu(II) and Zn(II) binding to histatin 1 and its hydrolytic products (histatin 1-2 and histatin 2), as well as to histatin 7 and histatin 9, and related thermodynamic and spectroscopic properties to *in vitro* activity. Histatins form stable metal complexes, with Cu(II) binding occurring primarily *via* the ATCUN motif in histatin 1 and histatin 1-2, and with Zn(II) coordination following the –HEXXH– motif. In contrast to simple electrostatic expectations, adding terminal Arg residues neither measurably stabilizes Zn(II) complexes nor enhances bactericidal activity. Across ATCC pathogens tested, activities remain modest and largely decoupled from complex stability, with only isolated effects upon metallation. Overall, two main conclusions may be drawn: (i) proteolysis mainly reshapes peptide topology and surface contacts rather than activating a metal-dependent mechanism and (ii) environmental pH together with anchoring to hydroxyapatite are likely the main drivers of efficacy *in situ*. We propose a working model in which site-selective hydrolysis positions histatins at the enamel–biofilm interface, while Cu(II)/Zn(II) binding acts as a structural governor rather than a direct antimicrobial switch. This reframes design rules for histatin-like therapeutics: optimize localization and pH-gated charge distribution first and then treat metallation as a context-dependent modulator.

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