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Copper-binding anticancer peptides from the piscidin family: an expanded mechanism that encompasses physical and chemical bilayer disruption

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In the search for novel broad-spectrum therapeutics to fight chronic infections, inflammation, and cancer, host defense peptides (HDPs) have garnered increasing interest. Characterizing their biologically-active conformations and minimum motifs for function represents a requisite step to developing them into efficacious and safe therapeutics. To investigate their structure, membrane location and permeabilization effects we employ solid state NMR, electrochemistry, neutron reflectometry, and lipid oxidation measurements. Our testing ground features piscidins 1 and 3 (P1/3), two amphipathic, histidine-rich HDPs that are α-helical bound to membranes and are naturally designed to carry metal ions through an amino-terminal Copper/Nickel binding motif. Mechanistically, we find that the metallated peptides not only physically but also chemically damage lipid membranes. With patch-clamp measurements on the inner Escherichia coli membranes, we also show that (P1/3) substantially decrease the activating tension for bacterial mechanosensitive channels. This indicated that the peptides can cause lipid redistribution and restructuring in the microenvironment near proteins. Furthermore, we demonstrate that metallating HDPs is an additional strategy to improve their cytotoxicity on cancer cells, though lipid oxidation effects. These unprecedented studies provide evidence that the mechanism of piscidins, in particular, and HDPs, in general, extends beyond simple membrane destabilization, helping to rationalize their broader spectrum of pharmacological effects.

Biography

Dr. Ella Mihailescu's research is focused on developing biophysical methods for investigations of the structural interactions of membrane proteins, membrane-active peptides, and lipophilic drug molecules with lipid membranes. A major effort in the Mihailescu laboratory is directed toward advancing precision measurement of membrane protein structures in engineered lipid platforms. She specializes in neutron scattering techniques.