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ABSTRACT BOOK

Ni(II) BINDING TO THE HUMAN TOOL LIKE RECEPTOR (HTLR4)

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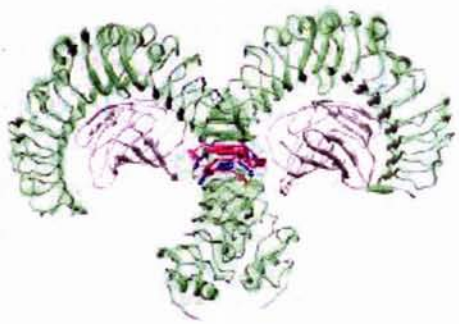
Nickel allergy is the most frequent cause of contact hypersensitivity (burning, redness, itching, swelling and even blisters) in industrialized countries, with 30% of population being affected. Contact allergy is commonly induced by nickel ions present in nickel-containing jewelry such as rings and earrings, as well as in nickel-containing cellular telephones. Ni(II) seems to trigger an inflammatory response by activating human Toll-like-Receptor 4 (hTLR4) [1-4]. Species-specific activation, as in this case, requires distinct sequence motifs that are present in humans but not in mouse, a species not sensitive to nickel-induced allergies. A sequence containing three histidine residues, H_{431}, and the non-conserved H_{456} and H_{458}, localized in the C-terminus, could be identified as the specific region of human TLR4 responsible for nickel responses. It has been proposed that the imidazole side chain of the histidine residues H_{456} and H_{458} may provide a potential binding site for this metal because they are located at an optimal distance to interact with Ni(II) ions, whereas H_{431} is located further apart. The aim of our research was to verify the possibility of metal binding to the sequence containing the three histidines supposedly involved in nickel response. The chosen segment was the 32aa peptide FQH_{431}SNLKQMSEFSVFLSLRNLIYLDISH_{456}TH_{458}TR, which was studied in order to understand both its binding properties and the thermodynamic stability of its metal complexes. Formation equilibria of Ni(II) complexes have been investigated in aqueous solution and in a wide pH range. Protonation and complex-formation constants have been potentiometrically determined; complex-formation models and species stoichiometry have been checked by means of UV-Vis absorption and CD spectroscopy and investigation through multidimensional and eteronuclear NMR spectroscopy. The predominant species for a 1:1 peptide/Ni(II) molar ratio was obtained at physiological pH and showed an effective binding of the metal to the target sequence.



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