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**Citrate-dependent and Heparan Sulfate-mediated Cell Surface Retention of Cobra Cardiotoxin.** C.-J. Chen<sup>a,c</sup>, H.-H. Guan<sup>a,b</sup>, S.-C. Lee<sup>b</sup>, W.-g. Wu<sup>b</sup>, <sup>a</sup>Life Science Group, National Synchrotron Radiation Research Center, <sup>b</sup>Inst. of Bioinformatics and Structural Biology, <sup>c</sup>Dept. of Physics, National TsingHua Univ., Hsinchu 300, Taiwan.

Cell surface retention of biologically active ligands through heparin or heparan sulfate (HS) binding plays an important role in certain disease states and cell development. Anionic citrate is a major component of venom but its role in toxicity remains puzzling. By immobilizing Chinese hamster ovary cells in microcapillary tubes and heparin on sensor chips, we showed that HS-mediated cell retention of the major cardiotoxin (CTX) from cobra, CTX A3, near membrane surfaces is citrate dependent. The CTX A3-heparin hexasaccharide complex structure with a bound citrate at 2.4 Å-resolution revealed a molecular model for toxin retention in which heparin induced conformational changes of CTX A3 lead to citrate-mediated dimerization. The results suggest a novel role for venom citrate in biological activity and reveal a mechanism that explains cell retention of CTX A3 through HS-CTX interaction. The combined usage of the Surface Plasmon Resonance (SPR) method and the retention experiment in microcapillary provides the novel approach to address the dynamic features of the biological activities of protein-HS interaction that can not be acquired by crystallography alone.

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