3-2016

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**Recommended Citation**

Jia, Zhe; Ackroyd, Christine; Christensen, Kenneth; and Dominy, Brian, "Insights into the effect of metal ions and conformational change on binding between Protective Antigen and Tumor Endothelial Marker 8" (2016). *Chemistry Annual Research Symposium*. 4.  
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Insights into the effect of metal ions and conformational change on binding between Protective Antigen and Tumor Endothelial Marker 8

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Introduction

Anthrax toxin’s entry route

Fig.1 Anthrax toxin, the causative agent of anthrax, infects the host cells after the Protective Antigen (PA) binds to a cellular receptor. The two known receptors on human cell surface are called TEM8(ANTRX1) and CMG2(ANTRX2).

Anthrax receptors in human body

Fig.2 CMG2 is usually found only on normal tissues. The other receptor, Tumor Endothelial Marker 8 (TEM8), is over-expressed on tumor cells, and is reported to be a potential anticancer target.

Questions

How do PA interact with TEM8?
- Understanding the mechanism is the first step towards potential drug design.

How does the metal ion work?
- Experiments showed replacing metal ion can greatly change the binding affinity.

Can TEM8 have open/closed conformations?
- TEM8 is structurally similar to integrins, which can adopt open/closed conformation correlated with high/low binding affinity towards ligands.

Methods

Simulation Method
- Crystal structures: PA-CMG2 (1T6B) TEM8(3N2N)  
- Homology modeling: TOPMATCH and MODELLER  
- Molecular Dynamics: NAMD 2.10 GPU, 20ns x10reps  
- Data analysis: CHARMM, VMD and MATLAB.

Cu2+ interacts with MIDAS residues weaker than Mg2+ does, but it makes these residues interact stronger with PA in return.

Replacing metal ion mainly affects the residues close to the metal ion. Individual residues on TEM8 result from metal ion replacement.

Results

Effect of Metal Ion

Fig.5 Interaction energy between metal ion and residues on PA/TEM8 complex. Residues are on TEM8 if not marked on PA. Mg2+ interacts with all MIDAS residues stronger than Ca2+ does.

Table 1 Binding Free Energies (kcal/mol) calculated using MM/GBSA for PA-TEM8 Binding System. The standard error was estimated over the mean of 10 repeats. Simulation results showed same trends and similar variance as experimental data. MM/GBSA method reduced the error by more than 70%. The variance in entropy change can be omitted.

Effect of Metal Ion

Fig.6 Distance between metal ion and the six coordination oxygen atoms in MIDAS. Because Ca2+ is larger than Mg2+ in size, Ca2+ keeps a longer distance to all coordination oxygen atoms than Mg2+ does. This also explains the weaker interaction between Ca2+ and these residues.

Conformation Change

Fig.9 F205 is reported to be the key residue regulates the conformation change in integrins. A similar structure can be found in TEM8, but it stabilizes the open conformation for TEM8 in a similar way as it stabilizes integrins in the close conformation.

References


Acknowledgements

This research was supported by NSF Career Award MCB-0953783. The authors thank Palmetto Cluster maintenance team for their constant technical support. The authors also thank our colleagues from Dr. Steve Stuart and his research group for sharing their pearls of wisdom with us during the course of this research.