Anchor residues in protein-protein interactions

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Overview

- Background
- Methods
- Results
- Conclusions
Protein-Protein Interactions

- A protein-protein interaction is the process whereby proteins associate to form a complex.
- Intermolecular forces:
  - Electrostatics – interaction between two charges
  - Desolvation – removal of solvent
- Proteins encounter many potential binding partners, but are able to distinguish their unique substrate.
- How do proteins recognize binding partners?
- Goal: to study the mechanism of protein interactions
  - “Lock-and-key” vs “induced fit”

http://www.chemistry.wustl.edu/~edudev/LabTutorials/Carboxypeptidase/carboxypeptidase.html
http://www.kensbiorefs.com/cellchem.html
Sometimes having a good look help!

- Molecular dynamics (MD) simulations
  - Simulation of motion of atoms by solving Newton’s equations of motion
- Sampling of realistic trajectories – time evolution of position and velocity of particle
- Explicit solvent – individual solvent molecules
- Virtual experiment
- Can only be performed *in silico*!
Sometimes having a good look helps!
Summary of Biophysical Insight

- Bound side chain is deeply buried in complex
- The conformations move toward the crystal (bound) conformation
  - Seems to prefer bound conformation
- What is the significance?
  - Anchor: side chain that is fully buried in the bound complex
Anchors

- Change in solvent-accessible surface area: \( \Delta \text{SASA}^a(i) = \text{SASA}^a(i) - \text{SASA}^\alpha(\beta)(i) \)
- Residue with largest \( \Delta \text{SASA} \) and fully buried after binding
- Identify anchors in 39 protein-protein complexes
## Results

<table>
<thead>
<tr>
<th>Complex PDB ID code</th>
<th>Receptor/ligand (PDB ID code)</th>
<th>Anchor ResID</th>
<th>ΔSASA, Å²</th>
<th>ΔG&lt;sub&gt;i&lt;/sub&gt; (rank), kcal/mol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enzyme/inhibitor complexes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1PPE</td>
<td>Trypsin/CMT-I</td>
<td>Arg-5</td>
<td>205.9</td>
<td>−11.3 (1)</td>
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<tr>
<td>1AVW</td>
<td>Trypsin/soybean inhibitor</td>
<td>Arg-563</td>
<td>202.7</td>
<td>−13.2 (1)</td>
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<tr>
<td>1BRC</td>
<td>Trypsin/APPI (1AAP)</td>
<td>Arg-15</td>
<td>198.8</td>
<td>−11.9 (1)</td>
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<tr>
<td>1CGL</td>
<td>α-Chymotrypsinogen/PSTI</td>
<td>Tyr-18</td>
<td>186.7</td>
<td>−8.6 (1)</td>
</tr>
<tr>
<td>1TGS</td>
<td>Trypsinogen/PSTI</td>
<td>Lys-18</td>
<td>169.7</td>
<td>−11.9 (1)</td>
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<tr>
<td>1TAB</td>
<td>Trypsin/BBI</td>
<td>Lys-26</td>
<td>167.7</td>
<td>−10.5 (1)</td>
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<tr>
<td>2PTC</td>
<td>β-Trypsin/PTI</td>
<td>Lys-15</td>
<td>163.8</td>
<td>−9.9 (1)</td>
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<tr>
<td>2SIC</td>
<td>Subtilisin BPN/Inhibitor</td>
<td>Met-70</td>
<td>159.4</td>
<td>−6.8 (1)</td>
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<tr>
<td>1DFJ*</td>
<td>RI/ribonuclease A</td>
<td>Tyr-433</td>
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<td>2SN1</td>
<td>Subtilisin novo/C12 (2C12)</td>
<td>Ile-56</td>
<td>148.4</td>
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<tr>
<td>1UGH*</td>
<td>UDG/UGI</td>
<td>Leu-272</td>
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<td>1CHO</td>
<td>α-Chymotrypsin/OMTKY3</td>
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<td>−8.3 (1)</td>
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<tr>
<td>1ACB</td>
<td>α-Chymotrypsin/eglin C</td>
<td>Leu-45</td>
<td>132.5</td>
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<tr>
<td>2TEC</td>
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<td>α-Thrombin/hirudin</td>
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<td>1CSE</td>
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<td>1MAH</td>
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<td>1FSS</td>
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<td>Barnase/barstar (1A19)</td>
<td>Asp-39</td>
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<td>1DFJ</td>
<td>Ribonuclease inhibitor/ribonuclease A (7RSA)</td>
<td>Asn-67</td>
<td>69.1</td>
<td>−1 (15)</td>
</tr>
</tbody>
</table>
Molecular Dynamics Simulations

- 11 complexes (out of 39 studied) chosen for MD simulations
- Performed on crystal structure of unbound protein containing anchors
- Trajectories sampled at 2 ps intervals

\[
\text{rmsd} = \sqrt{\frac{1}{n} \sum_{i=1}^{n} |x_n - y_n|^2}
\]
Results

- Anchors spend 30-90% of time in states close to conformation in the bound complex
- Remember: simulations performed with unbound structure, so this preference for bound conformation occurs without the binding partner!
- Some have 2 or even 3 anchors that work cooperatively
- Can be in ligand or receptor

Blue = bound structure
Red = unbound structure
Green = dominant conformation

1BRC
Latches

- Partially solvent exposed (30-70%) side chains on the edge of the binding interface
- Relatively free to adjust
- “Latch” the complex together
- Two types:
  - One residue bonds with relatively rigid residue of other protein
  - Two flexible residues simultaneously induce optimal configuration (salt bridge)

http://noxclass.bioinf.mpi-sb.mpg.de/help.htm
Results: Latches

- Lys-92 blocks interface in unbound conformation, but moves away from interface
- Lys-126 moves closer to bound and will form salt bridge with Glu-59
- Lys-122 also forms a salt bridge with Glu-13

1A0O
Conclusions

- Protein-protein interaction mechanism has developed over ages
- Mechanism allows for proteins to bind to their unique substrates
  - Lock-and-key and induced fit!
  - Anchors provide specificity necessary for recognition
  - Latches provide stability by "cementing" the high-affinity complex
References


Questions?