Molecular modelling of SH2 domain-peptide interactions

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Before carrying out docking studies on a potential target, it is important to gain a thorough understanding of the system. We have been studying SH2 domain-peptide interactions as a model system using a variety of molecular modelling techniques.

SH2 domains are highly homologous phosphotyrosine-binding motifs of approximately one hundred amino acids found in a range of signal transduction proteins. Uncontrolled signalling through protein tyrosine pathways involving these SH2 domains can lead to a variety of disease states, meaning that the search for novel agents which can interrupt such pathways has become an intense field of research.

Although there has been much evidence to suggest that interactions involving SH2 domains occur in a substrate-specific manner, it has also recently been argued that the family of domains may be too highly homologous and structurally conserved to allow for the design of specific inhibitors lacking undesired effects.

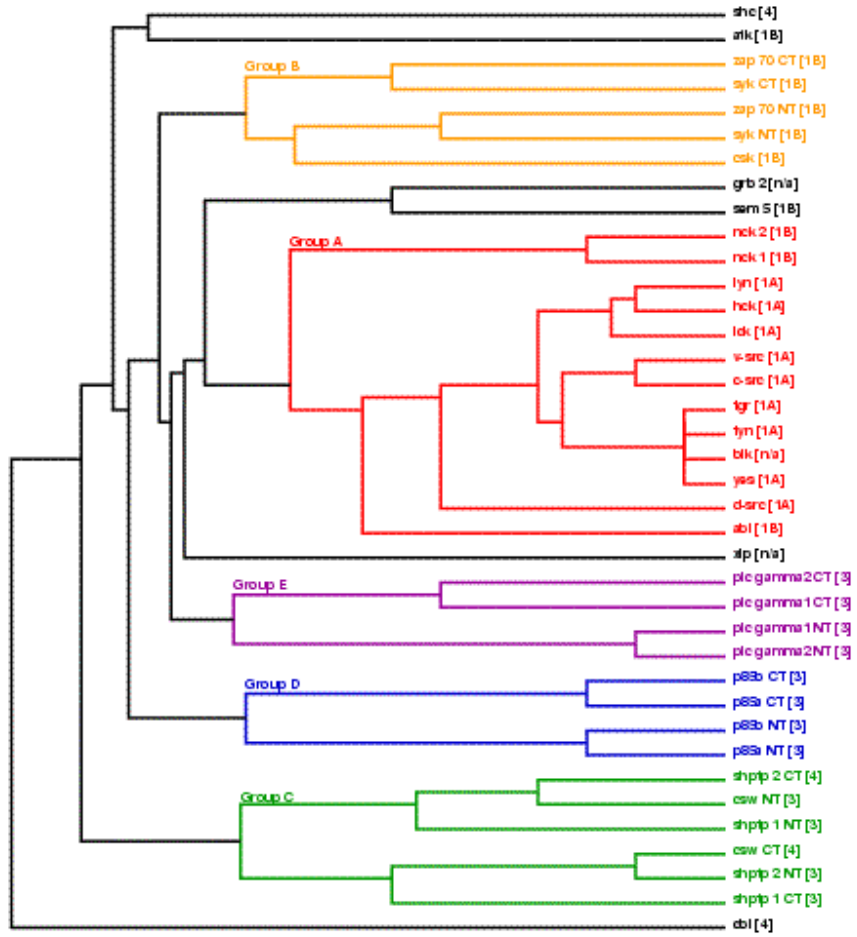

Figure 1: Clustering of Binding Sites. We have used the experimentally defined protein-ligand contacts to define the protein binding site, allowing the clustering of the domains according to amino acid conservation in the binding site.

The aim of our work has been to gain a greater understanding of the SH2 domain system by investigating these similarities and characterising the diversity within the family. This may allow us to determine residues which may be potentially exploitable in terms of structure-

based drug design. The main techniques we have been using include structural and sequence alignment, clustering of binding site residues (Fig. 1) and conservation studies (Fig. 2).
This study of conservation and diversity within the SH2 domain allows a greater understanding of the system, revealing regions that may be important in SH2 domain interactions.

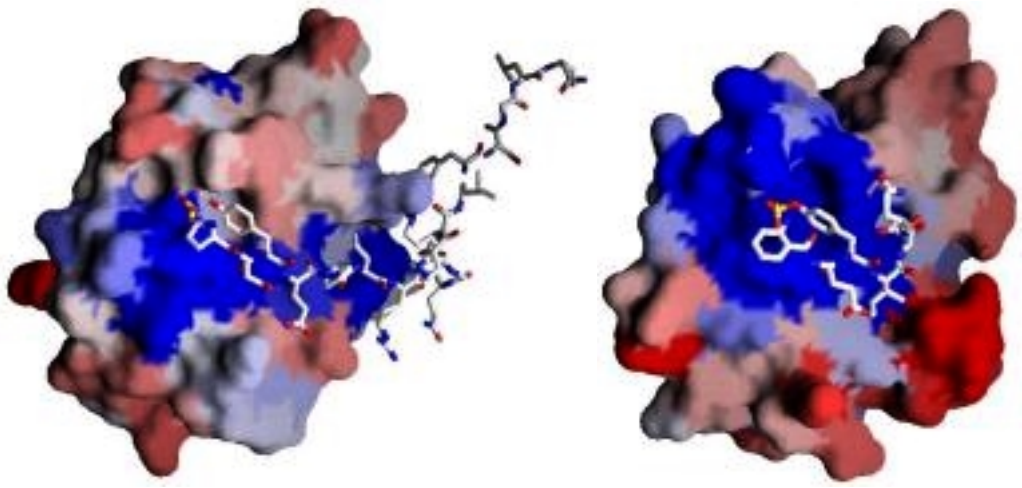

Figure 2: Conservation maps for SH2 domain subgroups Conservation is displayed on a representative SH2 domain structure for each sub-group. Blue indicates a high level of conservation and red indicates low conservation.

References

Campbell, S. J., & Jackson, R. M. (2002) Classification of SH2 domains according to similarity of binding site residues: A study of conservation and diversity within a family. *manuscript in preparation.*

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