Structural motifs recurring in different folds recognize the same ligand fragments

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Motivation

The structural analysis of protein ligand binding sites can provide information relevant for assigning functions to unknown proteins, to guide the drug discovery process and to infer relations among distant protein folds. Previous approaches to the comparative analysis of binding pockets have usually been focused either on the ligand or the protein component. Even though several useful observations have been made with these approaches they both have limitations. In the former case the analysis is restricted to binding pockets interacting with similar ligands, while in the latter it is difficult to systematically check whether the observed structural similarities have a functional significance.

Methods

Here we propose a novel methodology that simultaneously takes into account the structure of both the binding pocket and the ligand. We first look for local similarities in a set of binding pockets and then check whether the bound ligands, even if completely different, share a common fragment that can account for the presence of the structural motif. Thanks to this method we can identify structural motifs whose functional significance is explained by the presence of shared features in the interacting ligands.

Results

The application of this method to a large dataset of binding pockets allows the identification of recurring protein motifs that bind specific ligand fragments, even in the context of molecules with a different overall structure. In addition some of these motifs are present in a high number of evolutionarily unrelated proteins.

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