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How transient pockets open on the surface of the MDM2 protein

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The inhibition of protein-protein interactions is a promising strategy in anti-cancer therapy. A prominent example is the interaction between MDM2 and the tumor suppressor protein p53 that can be inhibited by small molecules identified in binding essays [1]. The structure-based design of such inhibitors suffers from the lack of well-defined binding pockets [2]. We therefore developed a pocket detection protocol that successfully identified transient pockets on protein surfaces. As the native inhibitor binding pocket was only partly detectable in unbound MDM2, this structure was used as starting point for 10 ns long molecular dynamics simulations. Trajectory snapshots were scanned for cavities on the protein surface using the PASS algorithm [3]. The detected cavities were clustered to determine several distinct transient pockets. They all opened within 2.5 ps and most of them appeared multiple times. At the native binding site, pockets of similar size as with a known inhibitor bound could be observed. AutoDock 3.0 [4] could successfully place an inhibitor molecule into these transient pockets with less than 2 Å RMS deviation from its crystal structure [5]. For understanding the underlying mechanisms of these pocket openings, the simulations were repeated in different solvent with and without restraints on the protein backbone atoms. Comparing the resulting transient pockets revealed fundamental differences in the number of pockets, their volume, their polarity and reflected the intrinsic influence of the backbone movements on the formation of surface pockets.

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