UNDERSTANDING P53, A PROTEIN "SHAPE SHIFTER" RESPONSIBLE FOR MANY CANCER TUMORS

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EXECUTIVE SUMMARY:

We used Blue Water's powerful GPUs, CPUs, and network to simulate p53, a key protein involved in cancer tumors, to better understand how it interacts with other key proteins in the cell. These simulations have taken p53 studies to unprecedented timescales, hundreds of microseconds to milliseconds, and have yielded new insight into p53 assembly. Specifically, we find that p53 plasticity with multiple proteins occurs via numerous pathways, suggesting specific challenges and opportunities for small molecule therapeutic approaches.

INTRODUCTION

We used Blue Waters for biomolecular simulations that study the folding and binding of the intrinsically disordered protein p53, which is a cancer tumor suppressor. Half of all known cancer tumors involve a mutation in p53, clearly making it a key protein in cancer. Beyond disease, p53 plays a key role in apoptosis, i.e. programmed cell death, the mechanism by which cells prevent disease by "shutting down" cells that have become old and problematic. Cancer cells are, in a sense, cells that didn't get this message to shut down and instead continue to grow in a damaged state. Activation of p53 prevents tumorgenesis and maintains normal cell growth. In this work, we studied the binding of a key portion of p53 to two proteins, s100β and a member of the sirtuin family, Sir2Tm, that antagonize the p53 activation pathway.

METHODS & RESULTS

We have used cutting-edge Markov State Model sampling methods combined with the vast power of Blue Waters to access unprecedented timescales, modeling phenomena on the millisecond timescale in all-atom detail.

This study gives biophysical insight into mechanisms for the assembly and binding of disordered proteins as p53 binds in two distinct structural conformations with the different binding partners. In the most probable pathways connecting the unfolded, unbound state and the folded, bound state, we find a fly-casting mechanism (first proposed by Peter G. Wolynes and collaborators) for both proteins, illustrated in Figures 1 and 2.

An initial capture process involves broad, mostly polar, protein contacts that allows flexibility for p53 rearrangement toward the bound state. For s100β, we see that p53 can rearrange into a stable misfolded off-pathway intermediate that may contribute the bottleneck rate for finding the native state. In both proteins, disordered regions on the p53 binding partner cooperatively shuttle the p53 peptide to the native, bound state. Understanding p53 interactions with these proteins can inform development of potential inhibitors for cancer therapy, to restore p53 activation and normal cell growth cycles in tumors. We suggest that the green interfaces highlighted in Figures 1 and 2 could be used to target p53 for small molecule or peptide inhibitors to prevent p53 capture.

WHY BLUE WATERS

Blue Waters is an extremely powerful and versatile computational resource. In addition to powerful CPU and GPU hardware, the fast interconnect allows us to do types of calculations (rapid adaptive sampling, Markov State Model construction, force field optimization, etc.) that we could not do on other platforms, such as distributed resources like Folding@home.

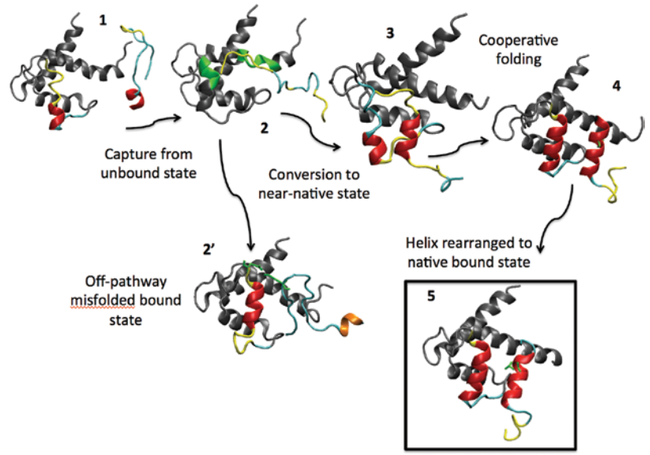

FIGURE 1: p53-s100beta predominant folding pathway. The proposed fly-casting-like mechanism involves initial capture by broad polar interfaces (green in state 2), followed by cooperative folding of p53 and Helix 3 of s100beta. p53 rearranges to the native folded, bound state, inserting L383 (green residue 5) into the hydrophobic pocket of s100beta. An off-pathway misfolded state is also identified, captured by a non-native salt bridge (green in state 2').

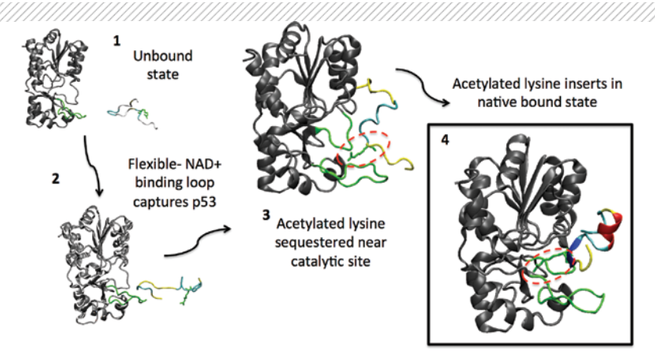

FIGURE 2: p53-sirtuin predominant folding pathway. The proposed fly-casting-like mechanism involves initial capture by flexible loops that also bind the cofactor NAD+ and involves broad polar interfaces (green in states 2 and 3). The acetylated lysine K382 (shown in red dashed circle) is shuttled via these flexible loops into the hydrophobic catalytic site, and its flanking residues form beta strands that staple two domains of sirtuin.