observed to interfere with signaling in breast-cancer cells by inducing non-Heme Coordination Versatility in a Truncated Hemoglobin

dimer demonstrates decreased stability compared to the horse cytochrome c similar structure and sequence, the domain swapped yeast iso-1-cytochrome c hinge loops relative to the horse cytochrome c dimer. Even though they contain an increased distance between the heme groups and an altered angle of the hinge loop. Interestingly, conversion of the heme crevice loop to the hinge loop results in a loss of the native Met80-heme ligation. This produces an open heme coordination site on each subunit of the dimer. As cytochrome c requires an open heme coordination site to act as a peroxidase, to oxidize cardiolipin and initiate the intrinsic apoptotic pathway, this dimer structure could potentially be a structure particularly suited to function in oxidizing cardiolipin. Here we present a crystal structure of a C-terminal domain swapped dimer in yeast iso-1-cytochrome c. In this structure the C-terminal alpha helix from one monomer positions itself in the native position of the opposite monomer and vice versa. The highly dynamic heme crevice loop, the most highly conserved portion of the cytochrome c sequence, spans the gap acting as the hinge loop. Displacement of His E10 by an exogenous ligand (e.g., cyanide in the ferric state) drives a significant conformational change allowing Ty22 (B10), Gln43 (E7) and Gln47 (E11) to establish a hydrogen bond network stabilizing the distal ligand.

The C-terminal domain swapped hemoglobin from Chlamydomonas reinhardtii, also binds cyanide and forms the same network of interactions. However, in the absence of an exogenous ligand, the neutral amino group of Lys53 (E10) coordinates the heme iron on the distal side. Displacement of His E10 by an exogenous ligand (e.g., cyanide in the ferric state) drives a significant conformational change allowing Ty22 (B10), Gln43 (E7) and Gln47 (E11) to establish a hydrogen bond network stabilizing the distal ligand.

The inhibition of the first calcium and integrin binding protein, CIB1 has been observed to interfere with signaling in breast-cancer cells by inhibiting non-apoptotic cancer cell death without harming healthy cells. This has led to a push for creating targeted therapy drugs which inhibit the CIB1 protein. While inhibiting CIB1 kills cancer cells, inhibiting the second protein, CIB2, could lead to hearing loss or deafness. Since CIB2 and CIB1 share similar sequences, I wanted to determine whether CIB2 could be inhibited by the potential targeted therapy drugs used to inhibit CIB1. Since no structure for CIB2 exists, I first created a homology model for the peptide-binding sequence for CIB2 onto the 2LM5 PDB structure of CIB1. This model was relaxed using Discrete Molecular Dynamics and analyzed for stability. Maestro and Peptide Docking simulations were then used to examine the model for druggable sites and association sites. The druggable sites were used for virtual screening with MedusaDock, where the results for CIB2 were to be compared to a previous virtual screening done for CIB1. Any drugs that were found to bind to both proteins would be excluded as targeted therapy candidates. By analyzing the model I was able to determine that CIB2 has one bipartite druggable site and two peptide association sites. Since the peptide association sites and druggable site on CIB2 were different in location and composition to the peptide and druggable site on CIB1, I concluded that the targeted therapy drugs created for CIB1 will have no effect on the functioning of CIB2. In the future, my lab intends to determine which association site on CIB2 corresponds to the actual peptide-binding site, as well as analyze the virtual screening results and experimentally validate the data from our simulations.

Heme Coordination Versatility in a Truncated Hemoglobin

Modeling the Calcium and Integrin Binding Protein 2

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