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Inhibitor Binding Induced Conformational Changes in the Cytochrome bc_1 Complex Suggest a Mechanism for the Capture-and-Release of the Iron-Sulfur Protein Subunit. Di Xia¹, Lothar Esser¹, Chang-An Yu² ¹Laboratory of Cell Biology, Center for Cancer Research, National Cancer Inst., NIH, DHHS. ²Dept. of Biochemistry, Oklahoma State Univ.

Most biological proton pumps are membrane channels, but the cytochrome bc_1 complex (bc_1) employs a different pumping mechanism by shuttling protons across the membrane and couples the proton pumping to electron transfer (ET). The bc_1 complex is an essential component of the cellular respiratory chain and the photosynthetic machinery; it catalyzes the reaction of ET from quinol to cytochrome c and concomitantly translocates protons across the membrane to generate a proton gradient for various cellular functions including ATP synthesis. Existing as a dimer in the mitochondrial inner membrane, the bovine bc_1 consists of 11 different subunits and have a molecular mass near 500 kDa. Three subunits, the cytochrome b (cyt. b), cytochrome c_1 , and the iron-sulfur protein (ISP), are considered important for the ET function. The mechanism of ET of bc_1 was investigated crystallographically by co-crystallizing bc_1 with many inhibitors. Dramatic conformational transitions from a fixed- to a free- state have been observed on the part of ISP subunit in response to binding of different inhibitors. Residues and secondary structure elements in the cyt. b subunit capable of discriminating bindings of different classes of inhibitors were identified. Together with biochemical investigations, the conformational changes correlate well with the model of ET mechanism of the bc_1 complex.