Identification and Characterization of Two Amino Acids Critical for the Substrate Inhibition of Human Dehydroepiandrosterone Sulfotransferase (SULT2A1)

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Substrate inhibition is a characteristic feature of many cytosolic sulfotransferases. Structural comparison among complex structures with various substrates reveals the detailed mechanism of substrate inhibition, and then deduces the roles of regulatory residues, Met137 and Tyr238, respectively (Fig. 1A, B). The crystal structures of M137I and M137W provide the structural insight into stereo effect of Met137, which regulates the substrate binding orientation (Fig. 2). The X-ray diffraction data were collected using synchrotron radiations at NSRRC BL13B beam lines.

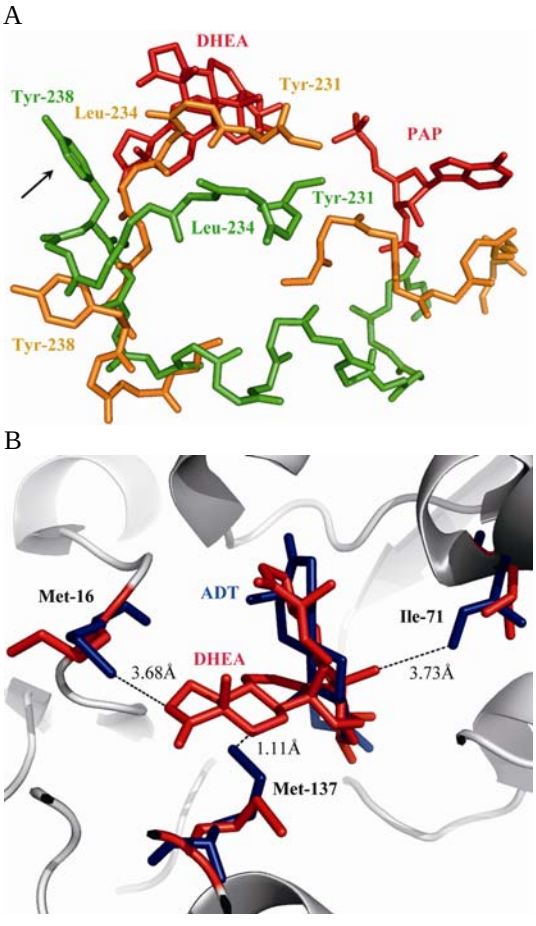

Figure 1. A, Structural alignment of the loop from residues Tyr-231 to Gly-252 of SULT2A1/PAP and SULT2A1/DHEA complexes. The Tyr238 plays the role of gate residue to regulate the substrate entry. B, Binding modes of DHEA and ADT molecules in SULT2A1. The Met137 regulates binding orientations and number of various sbstrates in each complex structure.

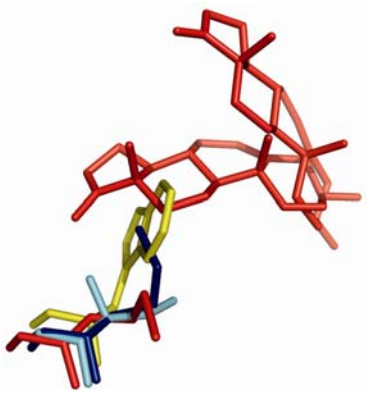

Figure 2. Superimposition of the solved structures of wild-type, M137I, and M137W SULT2A1. Met137 obviously mediates the substrate binding orientations and further regulates substrate inhibition.

The crystal structure of M137I and M137W SULT2A1 has been determined at 2.59 and 3.0 Å resolution, respectively.

The structural study of M137I and M137W SULT2A1 provides structural basis for enzymatic mechanism of substrate inhibition. M137I provides much larger space in the binding site, and M137W, however, even clashes with the modeled substrate. It consist with our kinetic data and we propose that Tyr238 regulates the release of bound substrate, and Met137 controls substrate binding orientation in SULT2A1. In addition, a corresponding residue in other cytosolic sulfotransferases was shown to have a function similar to that of Tyr238 in SULT2A1.