Analysis of MCT2 as a Selective Therapeutic Target in Cancer Metabolism

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The main feature of cancer is that the cell's normal metabolic process has changed to allow for uncontrolled growth. Monocarboxylate transporter 2 (MCT2, encoded by SLC16A7) is responsible for transporting lactate and pyruvate across the plasma membrane at high affinity. MCT2 relies on the presence of the chaperone protein embigin for both correct localization in membranes and for maintaining functional integrity. Although several members of the monocarboxylate transporter family have been shown to contribute to cancer progression, the relationship of MCT2 to both structure and therapy in cancer is currently very underdeveloped. We explore MCT2's implications for cancer prognosis and assess whether it can serve as a new metabolic drug target. We analyzed publicly available datasets of cancers to demonstrate SLC16A7 dysregulation within different types of cancers and association with overall survival. Alpha-Fold Multimer models were developed to produce a high-confidence model of the MCT2-embigin complex. Structural interface analysis was performed to identify hotspot residues involved in the critical protein-protein interactions within this complex. Alanine substitution docking simulations demonstrated that disruption of these interfaces would selectively disrupt contact within the complex, thus identifying structurally weak areas within the complex. Using over 1,600 drugs approved by the FDA to dock against structurally defined sites in MCT2, we were able to identify drugs that could be repurposed as potential inhibitors of MCT2. This represents the first comprehensive clinical and structural evaluation of MCT2 in cancer and nominates MCT2 as a novel therapeutic target for cancer treatment.

Awards Won: