MSDC-0160 and MSDC-0602 Binding with Human Mitochondrial Pyruvate Carrier (MPC) 1 and 2 Heterodimer: PPARγ Activating and Sparing TZDs as Therapeutics

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ABSTRACT

The mitochondrial pyruvate carrier (MPC) is a novel target for therapeutic drugs to treat Alzheimer’s and Parkinson’s disease, diabetes mellitus, and non-alcoholic steatohepatitis (NASH). Metabolic Solutions Development Company (MSDC) has two thiazolidinediones, MSDC-0160 and MSDC-0602, in the pipeline. This report describes results for a MPC1/2 heterodimer homology model. The FASTA sequences for MPC1 and MPC2 were accessed from UniProt and submitted to RaptorX, resulting in best candidate monomeric “protein data base” files for each. One mutant form of MPC1, L36I, was also processed. These were submitted to PyDock to generate best candidate MPC1/2 heterodimer models that were used for ligand docking analyses with AutoDock Vina and “Rosetta Online Server that Includes Everyone” (ROSIE). Multiple binding sites for pyruvate and both drugs were found on both MPC1 and MPC2 subunits with drugs having nearly double the affinity in each case except the intermediate and open-in states for the L36I mutant transporter.

KEYWORDS

Protein Homology Modeling, Inhibitor Docking, L36I Mutant, Michael Addition, MPC1, MPC2, Protein Protein Docking, Pyruvate, Single Nucleotide Polymorphism, Thiohemiacetal, UK-5099, Wild Type

INTRODUCTION

The mitochondrial pyruvate carrier (MPC) had been studied extensively in the 1970s through 1990s by two lab groups primarily, Andrew Halestrap and Katarzyna Nałęcz, providing many predictions on the functional protein structure and the mechanism of substrate binding. (Halestrap, A P, Denton, 1974; Halestrap, 1975, 1976, 1978a, 1978b; Hildyard, Åmmålå, Dukes, Thomson, & Halestrap, 2005; K. Nałęcz, 1994; Nałęcz, Kamińska, Nałęcz, & Azzi, 1992; K. A. Nałęcz, Müller, Zambrowicz, Wojtczak, & Azzi, 1990; M. J. Nałęcz et al., 1986) The two genes for MPC had been identified in 2012, along with evidence for pyruvate transport, but there was still doubt as to whether an MPC1 – MPC2 complex within the inner mitochondrial membrane (IMM) had pyruvate transport abilities.
(Bricker et al., 2012; Halestrap, 2012; Herzig et al., 2012). Recently, Halestrap and coworkers have utilized homology modeling and molecular dynamic simulations to generate 3 dimensional models of proton-linked monocarboxylate transporters (MCTs) and to identify key amino acid residues in the transport cargo and blocker binding sites (Manoharan, Wilson, Sessions, & Halestrap, 2006; Nancolas, Sessions, & Halestrap, 2015; Wilson, Meredith, Bunnun, Sessions, & Halestrap, 2009). Likewise, for MPC, still since 2012, no crystal structure has yet been registered or deposited in a protein data bank (PDB); and thus, a similar approach is reasonable. One homology model of the MPC1/2 heterodimer has been proposed using the bacterial semiSWEET (4QND.PDB) transporter as a template with indications of residues involved in the ligand binding site (Vanderperre, Bender, Kunji, & Martinou, 2015). This present report describes results for another MPC1/2 heterodimer homology model, based on a template using the E. coli respiratory complex I membrane domain B (3RKO.PDB), residues 242-366 and rmsd ranging from 2 to 9 Å. Along with the ligand docking results, this model is entirely consistent with and supports the hypothetical models proposed by both Halestrap and Nałecz (Halestrap, 1978a, 1978b; K. Nałecz, 1994). The predicted amino acid sequences for human MPC1 and MPC2 from UniProt (Bateman et al., 2015) were used.

Inhibition of the MPC as a novel therapeutic target is being tested currently at Phase 2 (MSDC-0160; NCT01374438) (Shah et al., 2014) clinical trial focused on progression from mild cognitive impairment to dementia of Alzheimer’s disease, (MSDC-0602; NCT02784444) for non-alcoholic steato-hepatitis (NASH) (Chen et al., 2012; McCommis, Hodges, Brunt, et al., 2016), and diabetes mellitus (MSDC-0160; NCT00760578) (Colca, VanderLugt et al., 2013) and soon for Parkinson’s disease (MSDC-0160) (Ghosh et al., 2016). Another study on treatment to delay onset of Alzheimer’s disease is in Phase 3 (pioglitazone, aka AD-4833; NCT01931566) (Crenshaw et al., 2015) and there is some evidence that it can bind MPC but that is not the stated target for this treatment. Thiazolidinediones (TZDs), pioglitazone (a peroxisome proliferator-activated receptor-gamma, PPARγ, agonist) and MSDC-0160 and MSDC-0602 (PPARγ-sparing TZDs) (Chen et al., 2012), are the drugs being tested. Thus, any new information and insight on the mechanisms of actions of these drugs are valuable and the 3D standard data file (SDF) formats, required for ligand docking in silico, are available for each of these drugs, as well as most of the classical inhibitors used in the very early biochemical studies. This study focuses only on the two MSDC drugs.

Thirty four non-synonymous single nucleotide polymorphisms (nsSNPs, or missense mutations) https://www.ncbi.nlm.nih.gov/SNP/SNP_ref.cgi?locusId=51660 are posted for human MPC1 while human MPC2 has 37 nsSNPs listed on the NCBI dbSNP https://www.ncbi.nlm.nih.gov/SNP/SNP_ref.cgi?locusId=25874 Short Genetic Variations page. Recently, in 2016, an online large-scale reference data set of human genetic variation, generated as part of the Exome Aggregation Consortium (ExAC), has become available and contains an aggregation and analysis of high-quality exome (protein-coding region) DNA sequence data on SNPs for 60,706 individuals of diverse ancestries. (Lek et al., 2016) The nsSNP for MPC1 gene of highest allele frequency in this population of humans was leucine substituted by isoleucine in the 36th amino acid residue (L36I) at 0.01675 (Figure 1). Therefore, this nsSNP was also modeled and tested for binding properties.

Other than that hypothetical data from biochemical analyses during the 1970s-1990s showing a critical role for an even number of cysteine residues, likely forming thiohemiacetal bonds with transporter substrate (Egger et al., 2012; Halestrap, 1978a, 1978b; K. Nałecz, 1994; Zarate-Romero, Murillo-Melo, Mujica-Jimenez, Montiel, & Munoz-Clares, 2016), along with arginine and possibly histidine and lysine residues (Denton & Halestrap, 1979), no conclusive structural evidence has yet appeared in the literature for studies of the pyruvate and inhibitor interactions with MPC1&2. Colca and coworkers have demonstrated that their specialized TZD photoprobe, MSDC-1101, binds to fruit fly and rat MPC2 and can be competitively blocked by MSDC-0602 and MSDC-0160 (Colca, McDonald, et al., 2013). Regardless, this complicated molecular approach provides no definitive evidence about the binding sites for these drugs in the MPC complex, i.e., human MPC, in particular relative to the binding site for pyruvate. There are some existing 3D crystal structures of pyruvate
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