TRIOSEPHOSPHATE ISOMERASE (TPI) A DIMERIC GLYCOLYTIC ENZYME AS A MODEL OF TIM-BARREL ACTIVE-SITE STRUCTURAL AND CHEMICAL ASPECTS IN THE MONOMER LOOP REGION'S REVERSIBLE CATALYTIC REACTION.

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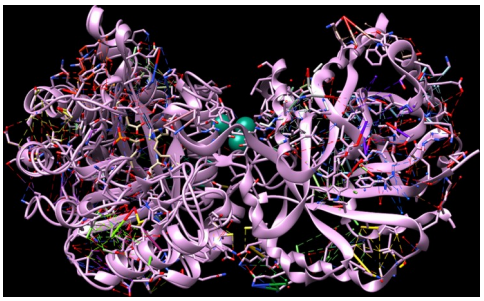
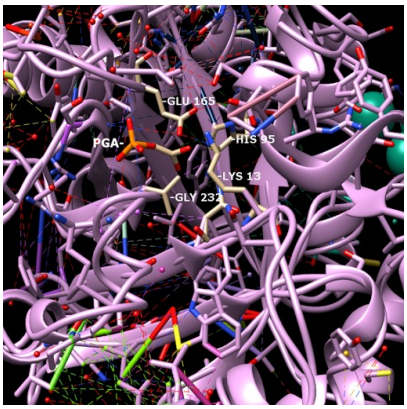
Triosephosphate isomerase (TPI, EC 5.3.1.1) is essential to glycolysis, catalyzes the fifth step in the glycolysis pathway the reversible conversion of dihydroxyacetone phosphate (DHAP) into glyceraldehyde-3-phosphate. TPI is a homodimer formed by two identical dimeric molecules of a single structural locus : 12p13.31.[1] TPI has only 1 functional gene with a molecular mass of 29 kDa, that after refinement are products of a distinct single[2] structural locus. The variant phenotype of identical subunits are expressed in both red cells and circulating lymphocytes,[3] catalyzing the interconversion of one of the two products breakdown by reversible[4] conversion. The TPI substrate by deprotonation[5] the transition state reaction of dihydroxyacetone phosphate (DHAP)[6] substrate yields one product of the glycolytic pathway, is a trend*[7] (Kcat) that persists creating the initial complex microcompartmentation of TPI to give (G3P)[8] glyceraldehyde-3-phosphate which seems to be the isomerase*[9] activity, release is slower than its conversion to DHAP in normal and TPI deficient cells. TIM[10] with its natural substrates has not been[11] (•) crystalized**.[12] TPI is a dimeric enzyme and contains 7 exons interrupted by six introns.



The crystallographic structure of (HsTPI) human triosephosphate isomerase PDB:1HTI is one dimer per asymmetric unit subunit 1 and subunit 2 are in the open and closed conformations in the 3-dimensional asymmetric space group P 2(1) which is specific to the Monoclinic with minimization on the entire structure in the presence of substrate analogues and its surrounding residues supporting possible regions targeted for drug design.

TPI deficiency (TPID) a disorder of glycolysis, occurring in haplotypes of specific alleles heterogeneous to clinical TPI[13]-deficiency,[14] with a rare homozygous deficiency[15] the resulting genetic[16] defect is the cause of a null variant incompatible with life[17] by abnormally high levels[18] of DHAP[19] which degrades spontaneously into the toxic (MG)[20] methylglyoxal,[21] due to deamidation[22] of asparagine (Asn15-71)[23] to form[24] aspartic and glutamic acid. Loop 6[25] plays a role in preventing the breakdown yield of methylglyoxal[26] (fMG)[27] one of the of the three products of enzyme-bound enediol(ate) phosphate,[28] towards elimination[29] of (fMG)[30] inorganic phosphate. TPI deficiency is due to the common aberrant dimerization (or the dissociation into inactive monomers) of mutation TPI 1591C,[31] encoding a Glu104-to-Asp[32] (glutamate-to-aspartate) substitution in the TPI variant[33] found in cases of hemolytic anemia coupled[34] with neurodegeneration,[35] the Glu104-to-Asp[36] substitution is the most common[37] disease allele inherited, when compared to wild-type TPI's three[38] (residues from the same subunit)[39] similar but not identical interactions between the inhibitor and catalytic residues, Glu 167[40] (or 165)[41] forms a stable dimer and provides the rationale[42] for production of structurally normal enzyme in humans, the E104D[43] mutation, provides the amyloid-resistant[44] structure of human triosephosphate isomerase (HsTPI).[45] Water-protein[46] molecules join[47] two catalytically active monomers which is only in its dimeric form, as monomers[48] of TIM are not functional. Within a hydrophobic catalytic pocket[49] of the native enzymes the binding and catalysis of TPIs in hemolysates,[50] bind to the red cell[51] membrane. Molecular modeling using the human crystal structure

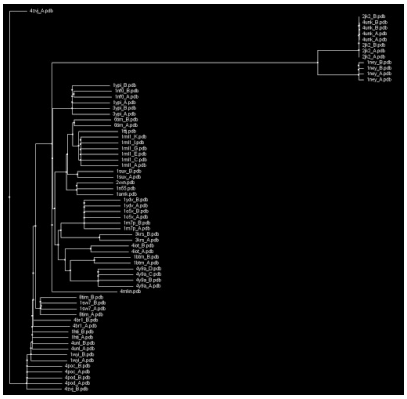
of TPI[52] was performed to determine how these mutations could affect enzyme structure and function. The Amyloid secondary[53] structure autoepitopes antigen-driven[54] mechanism works toward recovery of the anti-triosephosphate[55] isomerase mutant TPI peptide**[56] antigens. This is the scheme[57] that allows function-enhancing stability most significantly, the catalysis for deprotonation of DHAP or vice-versa GAP substrates of the TIM-barrel relative to TPI toward turnover of two-part substrate glycolaldehyde / phosphite dianion {GA + HPO32* the transition state for this enolising enzyme substrate pieces.} Km/obsd*[58] group of the whole GAP substrate and H95[59] (loop 4)[60] is also optimal for small mutational changes in or reflects its compatibility with amino acid residues which stabilizes the enediolate intermediate (GA/HPO)[61] activity from change in the products scheme[62] (a proton transfer mechanism)[63] DHAP/G3P[64] or interconversion of these intermediates.



Closed (activated for catalysis) of optimal WT (TPI) molecular modeling PDB 1HTI_B using the human crystal structure of TPI human triosephosphate isomerase (HsTPI) conformation 1hti_b, calculated to the incidence residue Water-protein molecules and the protein cage that interacts within a hydrophobic catalytic pocket isolated and examined which coded for human triose-phosphate isomerase. [EC: 5.3.1.1]….

The active flexible site loop must open[65] before product release,[66] unliganded in trypanosomal Tb[67]-TIM[68] glycerol phosphate ester to liganded Glu167[69] in the catalytic cycle and the enzymes substrate transition state between open and closed[70] to protect the substrate for the turnover of DHAP and G3P (GAP) the natural substrates, and inhibiting the formation of a toxic[71] by-product in the absence[72] of this equilibration reactions between dihydroxyacetone phosphate and glyceraldehyde 3-phosphate (G3P)[73] enzymes by mutations that impair biosynthesis transforming competent cells, in the presence of an auxotrophic[74] effect with these differences generated for an inability of the host organism to synthesize an essential[75] compound during glycolysis in Tb-TIM. Trypanosomal-TIM is a glycolytic enzyme essential for the parasite survival[76] that causes Chagas*[77] disease, in this study G. bellum[78] from the genus related Geraniaceae and its phenolic compound are leads which generates an unstable epimer[79] of an enzyme Geranin[80] A-containing changes resulting from ligand[81] adducts in the active site to capture in addition a source[82] of frustration[83] that becomes more favourable. Glycolaldehyde[84] (GA)[85] the simplest sugar-related molecules uptake of a proton by Glu167 preserves the small effect for inhibition by PGA (transition-state analog) relative to[86] substrate, G3P produces a triosephosphate isomerase with wild-type activity, loop 6[87] adopts the "closed" desolvated[88' 89] conformation to facilitate[90] completion of catalysis by the formation of the › Michaelis-Menten[91] complex (on the ‹ micros-ms[92] › time scale) utilization yields further corrected calculations with corresponding (slower Kcat) motional rates*[93] Km. Increase's are discussed in the context of the significance (Enzyme kinetics\Kcat) and may be estimated where the 'single-substrate' is locked in a protein cage probably[94] because of an active[95] reaction site (loop 6)[96] movement to the transition state for deprotonation; which are the on-average opened (substrate binding and release) and closed (activated for catalysis) of both monomers optimal WT (wild type) TIM conformations. Lys-12[97] ‹ is expected to interact with both centers, where the enediol intermediate along with the catalytic glutamate[98] base and histidine-95[99] the catalytic electrophile stabalizes the reversible[100] reaction intermediate that polarizes the substrate DHAP[101] in the Michaelis[102] complex. Interconversion spans the C-terminal[103] end of the eight β-strands.[104] For catalysis to occur likley[105] a low pKa value transition from DHAP - for the enolase

reaction enzyme enhancement 'relative to[106] the nonenzymatic reaction - (Bound PGH[107] - phosphoglycolohydroxamate mimics the (closed form) negative polarization (•)[108] charge••,[109] while PGA[110] (2-phosphoglycolate) the positively charged residues in the two active conformation sites.) is similar for the two conformers' in the closed[111] conformation, on ligand[112] binding interacting with the reactive end's (β)[113] the deprotonated substrate-bound structures to be protonated by a single-base (Glu-165)[114] proton transfer^ mechanism.



Structure of human triose phosphate isomerase at the positions of introns in homologous TPI genes from a number of phylogenetically diverse species. The introns motif are identified as calculated in phylogeny.
Phylogenetic trees constructed on the basis of sequence comparisons for triosephosphate isomerases analysis, TIM sequences were constructed based phylogeny with similarity, to those adopting the same structural fold of interest from different species for the taxonomic groups and the K13M mutations involvement in the human triosephosphate isomerase gene family[115]...

Interactions in the loop regions combine the effects of His95 and Lys13 for Glu165 (loop 4, 1,[116] and 6) the three crucial catalytic residues in triose phosphate isomerase, all[117] form the enediol intermediate necessary for the interconversion reaction catalyzed by TIM resulting in the natural substrates G3P formation. The introns motif are identified as calculated in phylogenic motifs.[118] Poorly conserved residues as targets for specific••[119] drug design are expected when compared to (TPI)[120] Triosephosphate isomerase (•). Catalytic residues of the phylogenetic relationship pathways obtained by sequence based methods of specific key amino acids can than be calculated to the incidence residues and other TIMs which may influence the (human) HsTPI equilibrium.

Footnotes

Some Correlations are identified with Basic Punctuation or Bullet's: ^ ,* and •, ••.
Triosephosphate isomerase Mar 20, 2016 images: 7 – 3 MB

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