Dimeric Structure of Human Glutathione Transferase A1-1 is Stabilised by the Inter-Subunit Lock-and-Key Motif

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A major structural feature at the inter-subunit interface of human class Alpha GST (hGST A1-1) is the conserved hydrophobic lock-and-key motif. The Phe-52 key residue is an important structural moiety in modulating catalytic and ligandin functions and although not essential for dimerization, it maintains the conformational stability of the protein. It is proposed that the preceding Met-51 residue also constitutes the key of hGST A1-1 and hence also contributes to protein function and dimer stability. In an attempt to gain further insight into the interactions occurring at the inter-subunit of hGST A1-1, this study evaluates the contribution of the Met-51 residue, as well as both the Met-51 and Phe-52 residues, to protein function and dimer stability. Replacement of the Met-51 and Phe-52 key residues contributes significantly to protein function and dimer stability. However, disruption of the dimer interface is dependent upon the mutation introduced at the inter-subunit interface. The Met to Ala substitution alone impacted upon ligandin function only. Substitution of both the Met-51 and the Phe-52 key residues impacted dramatically upon the catalytic as well as the ligand binding properties. The urea-induced conformational stability studies further indicated destabilisation of the M51A and M51A/F52S proteins as a result of the amino acid substitutions at the key, with the replacement of both lock-and-key residues resulting in the formation in aggregate prone structures. The lock-and-key motif in hGST A1-1 is therefore not essential for the dimerization to occur, but it does stabilise the quaternary structure at the dimer interface. Clearly a properly configured interface is important for the stabilization and functionality of the enzyme.