Structure of Microsomal Prostaglandin E Synthase 1 as Determined by Electron Crystallography.

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We have determined the structure of human microsomal prostaglandin synthase 1 (MPGES1) in complex with the tripeptide γ-L-glutamyl-L-cysteinyl-glycine, glutathione (GSH) at 3.5 Å in-plane resolution using electron crystallography [1]. Pair wise acquisitions of electron diffraction patterns at a camera length of 200 cm were made. A tilted recording was followed by a 0º pattern which was used entirely for classification and quality assessment. The trimeric model of microsomal glutathione transferase 1 (MGST1) [2] was used for a molecular replacement search since the sequence identity between these proteins is high. A final structure of the MPGES1 trimer was obtained following numerous rounds of refinement using tight geometry restraints and medium non-crystallographic symmetry in REFMAC5 in combination with geometry idealisation and manual rebuilding in O. The subunits of MPGES1 form a homotrimer (here related by non crystallographic symmetry) in a similar way as for MGST1 [2], FLAP [3] and LTC4S [4,5], i.e. other structurally characterized members of the same superfamily. An omit map calculated between the observed electron diffraction amplitudes and amplitudes calculated from the protein model showed three distinct U-shaped densities corresponding to GSH. The thiol group of GSH is stabilized by an arginine residue directed between the observed electron diffraction amplitudes and amplitudes calculated from the protein model showed three distinct U-shaped densities corresponding to GSH. The thiol group of GSH is stabilized by an arginine residue directed...