acid residues and Fru-6P bound in the active site and in the Fru-2,6-P_2 effecttor site We have examined the consequesces on the enzyme structure and function of the two gene-duplication events that occured in the yeast gene compared to the prokatyotic gene.

Keywords: allostery, metabolism, regulation and reaction mechanisms of enzymes

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Molecular Basis for MSD and Catalytic Mechanism of the Human Formylglycine Generating Enzyme

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Sulfatases are enzymes essential for degradation and remodeling of sulfate esters. Formylglycine (FGly), the key catalytic residue in the active site, is unique to sulfatases. In higher eukaryotes, FGly is generated from a cysteine precursor by the FGly generating enzyme (FGE). Inactivity of FGE results in multiple sulfatase deficiency (MSD), a fatal autosomal recessive syndrome. We determined the FGE crystal structure by Ca^{2+}/Sulphur SAD phasing using in-house data collected at a wavelength of 1.54Å. Based on this structure, we report that FGE is a single-domain monomer with a surprising paucity of secondary structure and adopts a unique fold. The effect of all eighteen missense mutations found in MSD patients is explained by the FGE structure, providing a molecular basis of MSD. The catalytic mechanism of FGly generation was elucidated by six high-resolution structures of FGE in different redox environments. The structures allow formulation of a novel oxygenase mechanism whereby FGE utilizes molecular oxygen to generate FGly *via* a cysteine sulfenic acid intermediate [1].

[1] Dierks T., Dickmanns A., Preusser-Kunze A. Schmidt B., Mariappan M., von Figura K., Ficner R., Rudolph M.G., *Cell*, 2005, **121**, *in press.*

Keywords: enzyme catalytic mechanism, post-translational modification, genetic disease

MS51 COMPLEMENTARY APPROACHES TO BIOLOGICAL STRUCTURE DETERMINATION

Chairpersons: Wah Chiu, Lucia Banci

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Estimating Protein Fold using Wide-angle Solution Scattering Data

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The secondary and tertiary structure motifs of protein folds have characteristic distributions of inter-atomic distances that produce features buried within the x-ray scattering pattern from a protein in solution. We have demonstrated that wide-angle x-ray solution (WAXS) scattering contains rich details of the secondary, tertiary and quaternary structure of multiple classes of proteins. Uses to date include the observation of ligand-induced structural changes and the monitoring of fold stages during chemical and radiation-induced protein denaturation.

WAXS scattering patterns obtained at high flux third generation synchrotron beam lines are not only sensitive to protein conformation states, but the scattering patterns generated can be quantitatively compared to data calculated from detailed structural models derived from crystallographic data. This method can be applied to almost any protein in solution including membrane proteins, large protein complexes and proteins with substantially disordered regions. As such, WAXS has the potential for being a sensitive, global method for detecting ligand-induced structural changes in proteins, narrowly categorizing proteins based on their scattering homology to known folds and elucidating the differences between crystal structures and aqueous conformations.

Keywords: protein structure analysis, WAXS, macromolecular structures

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Cryo-electron Microscopy of the Ribosome: Methods of Fitting, and Inference of Dynamics

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Cryo-electron microscopy yields “three-dimensional snapshots” of the ribosome and its interaction with ligands at time points determined by the use of antibiotics or GTP analogs. If several such snapshots are available for one of the functional processes, how can we obtain a seamless picture of its dynamics? We address the two aspects of this problem: the interpretation of medium-resolution cryo-EM density in terms of published coordinates of structural components, and the means of “interpolating” between subsequent structures inferred from the snapshots. This problem is exemplified by the investigation of the decoding process, for which four 3D snapshots are available [1,2].

[1] Valle M. et al., *Nat. Struct. Biol.*, 2003, **10**, 899. [2] Frank J., Sengupta J., Gao H., Li W., Valle M., Zavialov A., Ehrenberg M., *FEBS Lett.*, 2005, **579**, 959.

Keywords: real-space refinement, MD simulation, decoding

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Structure of the Acrosomal Bundle, a Biological Machine, at 9.5 Å Resolution

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In the unactivated Limulus sperm, a 60 μm-long bundle of actin filaments crosslinked by scruin is bent and twisted into a coil around the base of the nucleus. At fertilization the bundle uncoils and fully extends in five seconds to support a finger of membrane, the acrosomal process. This biological spring is powered by stored elastic energy and does not require the action of motor proteins or actin polymerization. Our 9.5 Å electron cryomicroscopic structure of the extended bundle [1] shows that twist, tilt, and rotation of actin-scruin subunits deviate widely from a "standard" F-actin filament. This deviation appears to be related to the packing requirements of the scruin cross-linkers. The structural organization allows filaments to pack into a highly ordered and rigid bundle in the extended state, but also suggests a mechanism for storing and releasing energy between the coiled and extended states.

[1] Schmid M.F., Sherman M.B., Matsudaira P., Chiu W., *Nature*, 2004, **431**, 104.

Keywords: actin, electron microscopy, macromolecular crystallography protein structures

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Beyond the Structure: how to Deal with Structural Disorder

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Structural disorder in proteins is probably as precious as a source of information as the structure itself. In fact, disorder implies mobility. If we are able to translate what is observed as disorder, both in X-ray and NMR structures, into dynamics, we are in a better position to understand function. NMR is a powerful tool to analyse mobility in terms of time scales of motions, from seconds down to picoseconds.

Novel approaches on how to deal with disorder by NMR will be shown, with particular reference to metalloproteins. Examples will range from the study of conformational flexibility at the active site of