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The Structural Domains of the Early B-cell Factors (EBF). Marina I Siponen[a], Magdalena Wisniewska[a], Lari Lehtiö[b], Ida Johansson[a], Helena Berglund[a]. [a]*Structural Genomics Consortium, Department of Molecular Biochemistry and Biophysics, Karolinska Institutet, Stockholm, Sweden.* [b]*Division of Pharmacy, Department of Biochemistry and Pharmacy, Åbo Akademi University, Turku, Finland.*
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The human Early B-cell fctor (EBF) family of transcription factors plays a variety of developmental roles [1]. Roles for this four-member family of proteins (EBF1-4) include B-cell development in lymphopoiesis, neuronal development, ***osteogenesis*****,** and adipogenesis. Furthermore, recent studies have started identifying the absence of expressed EBFs in different cancer forms such as leukemias (EBF1) and glioblastomas (EBF3), suggesting a new tumor suppressor role for EBF family members [2]. The structured part of the EBFs is composed of a DNA binding domain (DBD), a TIG (transcription factor immunoglobulin) domain, and an atypical helix-loop-helix (HLH) region. An additional unstructured trans-activation domain is also present in the C-terminus. The EBF proteins show very high homology within the family over the whole structured part, consequently they can bind to specific DNA response elements as homo or hetero-dimers. Although the different domains have been, to a certain extent, biochemically characterized, no structural information was yet available for the EBF proteins. Structural data is of particular importance for this family since they share very low sequence similarity with other transcription factors. Using a domain approach, we have independently solved both the DBD and TIG+HLH domains of human EBF1 and EBF3, respectively. Despite low sequence similarity, the DBD structure reveals a striking resemblance to the DNA binding domains of the Rel homology superfamily of transcription factors. Interesting features of this domain include an atypical zinc binding site, termed Zn-knuckle, a region previously coined as important for specific DNA binding and transcriptional activation [3]. The TIG+HLH domain reveals an interesting dimerisation motif likely involved in protein-protein interactions, with either family members or regulatory partners.

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Keywords: Transcription regulation, Biochemistry of DNA proteins, X-ray protein crystallography

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Structural insight into *Neisseria meningitidis* PorB during pathogenesis. Mikio Tanabe[a], Crina Nimigean[b], Tina Iverson[c]. [a]*ZIKHALOmem, Martin-Luther-Universität Halle-Wittenberg, Institut für Biochemie und Biotechnologie, Halle(Saale), Germany.* [b]*Departments of Anesthesiology, Weill Cornell Medical College, New york, NY, USA.* [c]*Department of Pharmacology, Vanderbilt University Medical Center, Nashville, TN, USA.*
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PorB is the second most prevalent outer membrane protein in *Neisseria meningitidis*. PorB is required for bacterial survival and neisserial pathogenesis, but is also able to elicit a Toll-like receptor mediated host immune response. During infection, PorB can integrate into host cell mitochondria and likely binds mitochondrial ATP, which is thought to be important for cellular apoptosis. We have determined the x-ray crystal structure of PorB at 2.3 Å resolution. Structural analysis and co-crystallization with substrate molecule suggest three distinct putative solute translocation pathways (non-slective cation, non-selective anion and sugar specific) through the channel pore. Co-crystallization with the ATP analog AMP-PNP suggests that binding of nucleotides regulates these translocation pathways both by partial occlusion of the pore and by restricting the motion of a putative voltage gating loop. PorB, located on the surface of *N. meningitidis*, can be recognized by receptors of the host innate immune system during infection. Features of PorB suggest that Toll-like receptor mediated recognition of outer membrane proteins may be initiated by a non-specific electrostatic attraction.

Keywords: neisseria pathogenesis, outer membrane protein, solute transport

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Structure of the essential enzyme ThiM from the bacterium Staphylococcus *aureus.* Julia Drebes[a], Markus Perbandt[a,c], Carsten Wrenger[b], Christian Betzel[a]. [a]*University of Hamburg, Department of Chemistry, Laboratory for Structural Biology of Infection and Inflammation, c/o DESY, Germany.* [b]*Bernhard Nocht Institute for Tropical Medicine, Department of Biochemistry, Germany.* [c]*University Medical Center Hamburg-Eppendorf, Department of Medical Microbiology, Virology and Hygiene, Germany.*
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Staphylococcus aureus is a commensally existing bacterium that colonizes 20% of healthy adults permanently and up to 50% transiently. Its pathogenicity plays an important role in nosocomial infections affecting immuno-suppressed patients. Symptoms caused by *S. aureus* range from superficial skin lesions up to life threatening conditions like pneumonia or endocarditis [1]. In 2005, *S. aureus* remerged as a major human pathogen due to methicillin resistant *S. aureus* (MRSA) strains and caused more than 18,000 deaths in the U.S.A. Staphylococcal pneumonia contributed to more than 75% of these deaths [2]. Therefore the developement of new and effective drugs against S. aureus is urgently required. Attractive drug targets are preferably metabolitic pathways, which are absent in the host organism.
In terms of strcuture base drug design investigations we have characterized and analysed the structure of ThiM (5-(hydroxyethyl)-4-methylthiazole kinase) from Staphylococcus *aureus*, which is an essential enzyme of the vitamin B1 metabolism. Vitamin B1, in its active form thiamine pyrophosphate (TPP), is a cofactor for several other key enzymes of the carbohydrate and amino acid metabolism [3]. Humans have to acquire Vitamin B1 by dietary uptake, because the metabolic pathway is absent. We intent to analyse the structures of all enzymes involved in the vitamin B1 cascade to allow a most systematic development of potential drugs against S. aureus, Here we present structural insights of ThiM at 2.1 Å resolution.