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Review 1

Folding of β -barrel membrane proteins in lipid bilayers – Unassisted and assisted folding and insertion $\stackrel{\text{tr}}{\rightarrow}$ 3

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ABSTRACT

Article history: In cells, β -barrel membrane proteins are transported in unfolded form to an outer membrane into which they 19 Received 22 March 2015 Received in revised form 6 May 2015 10 Accepted 7 May 2015 Available online xxxx 11 04 Kevwords: 05 β -barrel membrane protein 14 Membrane protein folding

fold and insert. Model systems have been established to investigate the mechanisms of insertion and folding of 20 these versatile proteins into detergent micelles, lipid bilayers and even synthetic amphipathic polymers. In 21 these experiments, insertion into lipid membranes is initiated from unfolded forms that do not display residual 22 β -sheet secondary structure. These studies therefore have allowed the investigation of membrane protein folding 23 and insertion in great detail. Folding of β -barrel membrane proteins into lipid bilayers has been monitored from 24 unfolded forms by dilution of chaotropic denaturants that keep the protein unfolded as well as from unfolded 25 forms present in complexes with molecular chaperones from cells. This review is aimed to provide an overview 26 of the principles and mechanisms observed for the folding of *B*-barrel transmembrane proteins into lipid bilayers, 27 the importance of lipid-protein interactions and the function of molecular chaperones and folding assistants. This 28 article is part of a Special Issue entitled: Lipid-protein interactions. 29

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Kinetics Outer membrane

Periplasmic chaperone

BAM complex

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Abbreviations: C, cysteine; CAC, critical association concentration; CD, circular dichroism; diC_{10:0}PC, 1,2-dicapryl-sn-glycero-3-phosphocholine; diC_{12:0}PC, 1,2-dilauroyl-sn-glycero-3phosphocholine; diC_{12:0}PE, 1,2-dilauroyl-sn-glycero-3-phosphoethanolamine; diC_{12:0}PG, 1,2-lauroyl-sn-glycero-3-phosphoglycerol; diC_{14:0}PC, 1,2-dimyristoyl-sn-glycero-3phosphocholine; diC_{18:1}PC, 1,2-dioleoyl-sn-glycero-3-phosphocholine; diC_{18:1}PE, 1,2-dioleoyl-sn-glycero-3-phosphocholine; diC_{18:1}PC, 1,2-dioleoyl-sn-glycero-3-phosphochol F, phenylalanine; FomA, major outer membrane protein A from Fusobacterium nucleatum; hVDAC1, voltage-dependent anion-selective channel, human isoform 1; KTSE, Kinetics of Tertiary Structure Formation by Electrophoresis; LPS, lipopolysaccharide; LUVs, large unilamellar vesicles; OM, outer membrane; OmpA, OmpC, OmpF, OmpG, OmpT, OmpW, and OmpX, outer membrane proteins A, C, F, G, T, W, and X from Escherichia coli (see also Table 1); OMP, outer membrane protein; PAGE, polyacrylamide gel electrophoresis; PagP, lipid A palmitoyltransferase from E. coli; SDS, sodium dodecylsulfate; Skp, seventeen kilodalton protein; SurA, survival factor A; SUVs, small unilamellar vesicles; TM, transmembrane; TMP, transmembrane protein; TMD, transmembrane domain; VDAC, voltage-dependent anion-selective channel; W, tryptophan; wt, wild-type; Y, tyrosine

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Q6 1. Introduction

66 Biological membranes are essential structuring components of all living cells. The core elements of membranes are lipid bilayers and inte-67 gral and peripheral proteins. While a lipid bilayer constitutes the hydro-68 phobic barrier of a membrane and prevents the arbitrary exchange of 69 70 solutes, transmembrane proteins (TMPs)^a allow the regulated exchange 71 of solutes across the lipid bilayer or they transduce signals from one side of the membrane to the other. Many membrane proteins perform enzy-72matic reactions, which take place at the membrane-water interface. 73 Specific lipid-protein interactions are important for the stable integra-74 tion and activity of integral and peripheral membrane proteins (see, 7576e.g. [1-3]). The unique structure of the lipid bilayer requires specific 77 surface properties of integral and peripheral proteins that are necessary 78for their function. Protein surfaces exposed to the fatty core of the mem-79brane are typically hydrophobic, while protein surfaces exposed to the aqueous space usually are composed of polar amino acid residues. 80 81 These properties of membrane proteins have raised strong interest to examine the physical principles, how integral proteins fold and insert 82 into membranes (see, e.g., [4-7]). TMPs can be subdivided into two 83 classes according to their transmembrane (TM) structure, namely 84 85 α -helical TMPs and TMPs with β -sheet secondary structure in the lipid bilayer. While TMPs with a single TM helix are common [8], all 86 TMPs with β -sheet secondary structure known to date form closed 87 β -barrels with at least 8 antiparallel TM β -strands. In these β -barrels, 88 all β -strands are connected to their next neighbors through hydrogen 89 90 bonds between the amide-protons and the carbonyl groups of the poly-91peptide backbone. The β -barrel structure is closed through hydrogen bonds formed between the amino-terminal and the carboxy-terminal 92 93 membrane-spanning β -strands. The strands of β -barrel TMPs are connected by short periplasmic β -turns and by long loops facing the poly-9495saccharide region and the space outside the cell or cell organelle. The geometry of the β -strands and the necessity to form hydrogen bonds 96 between polar amide and carbonyl groups of the polypeptide chain 97 within the hydrophobic core of the membrane exclude that individual 98 β -strands can exist in a lipid bilayer. In the TM region of a β -barrel, 99 100 polar and apolar residues alternate with one another: the β -strands 101 are amphipathic. The hydrophobic residues face the apolar lipid phase, 102while polar residues face the barrel lumen, across which nutrients in aqueous solution are transported. Therefore in comparison to α -helical 103 TMPs, the average hydrophobicity of TM β -barrels is low. With the ex-104 ception of the capsule transporter Wza [9], all currently known outer 105membrane proteins (OMPs) from bacteria form β -barrel TM structure. 106 β -barrel TMPs are also found in the outer membranes (OMs) of mito-107 chondria and chloroplasts. Some representative examples are shown 108 in Fig. 1. *β*-barrel TMPs are characterized by the number of antiparallel 109 β -strands and by the shear number, which is a measure for the inclina-110 tion angle of the β -strands against the barrel axis [10]. The OMPs of 111 112 known crystal structure from bacteria form TM β -barrels with even 113 numbers of β -strands ranging from 8, like in the TM domain (TMD) of 114 outer membrane protein A (OmpA) from Escherichia coli, to 26 in the lipopolysaccharide (LPS) channel LptD. The voltage-dependent anion- 115 selective channel, human isoform 1 (hVDAC1) from mitochondria 116 forms a β -barrel with 19 TM strands. OMPs exist as monomers (for ex- 117 ample OmpA, BtuB), dimers (OmPIA) or trimers (ScrY, LamB). OMPs can 118 be grouped into at least 10 different categories regarding their function 119 [7,11]. They may serve as structural proteins (for example OmpA), as 120 toxin binding proteins (OmpX), as passive unspecific diffusion porines 121 (OmpF, OmpC), as specific porines (LamB, ScrY, FadL, Tsx), as active 122 transporters (BtuB, FhuA), as proteases (OmpT), lipases (OmPlA), or 123 acyltransferases (PagP), as adhesion proteins (NspA, OpcA), as insertion 124 machines (BamA), as pilus assembly plattforms (PapC, FimD), as export 125 channels (TolC), etc. Some OMPs of known crystal structure of their 126 β -barrel domains are listed in Table 1, together with their molecular 127 weights, pI, number of TM β -strands in the β -barrel domain, number 128 of amino acid residues, oligomeric state and function. In this review, 129 we provide an overview of the observations and biophysical principles 130 of folding and membrane insertion of β -barrel membrane proteins 131 into lipid bilayers of defined composition. 132

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2. Denaturation and refolding of β -barrels

OmpA is the first TMP for which successful refolding was shown. In 134 1978, Schweizer et al. [12] demonstrated that more than 90% of heat- 135 denatured OmpA (Omp II [13]) regained its native structure in the pres- 136 ence of LPS and Triton-X-100. Later, Dornmair et al. [14] established that 137 OmpA can refold in micelles of octylglucoside in the absence of LPS after 138 dilution of the denaturants, sodium dodecyl sulfate (SDS) or urea. Fur- 139 ther experiments demonstrated that urea-denatured OmpA can be 140 folded both in lipids and in a wide range of detergents, provided that 141 the concentration is above the CAC [15]. OmpA folds even from certain 142 fragments in micelles of octylglucoside [16,17], an observation first 143 made in vivo for separately expressed fragments [18]. Later, very large 144 β -barrel TMPs like the 22-stranded iron transporter FepA, which contains an additional domain in the barrel lumen, have been refolded suc- 146 cessfully from their denatured forms in chaotropic denaturants into 147 detergent micelles upon denaturant dilution [19]. The list of successfully 148 refolded β -barrels also includes the 19-stranded human VDAC from the 149 OM of mitochondria [20–23]. Interestingly, circular dichroism (CD) 150 spectra indicated that human VDAC, isoform 1, develops slightly differ- 151 ent secondary structure in LDAO detergent micelles than in lipid 152 bilayers of various phospholipids [20]. In LDAO/diC_{12:0}PC mixtures, the 153 β -sheet content decreased from ~37% in pure $diC_{12:0}PC$ bilayers to 154 ~32% in pure LDAO micelles, whereas the content of α -helical secondary 155 structure increased from ~11% to ~16%. A change of 5% in secondary 156 structure corresponds to about 14 residues out of 282 residues in 157 VDAC. This is not a very large fraction, but could be enough to form an 158 additional transmembrane β -strand at the expense of some of the 159 α -helical structure obtained for the detergent solubilized form. Expression of β -barrel TMPs in form of cytosolic inclusion bodies and subse- 161 quent refolding has in fact become a major strategy for the isolation 162 of many β -barrel TMPs (for a recent review, see e.g., Ref. [24]). A 163

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