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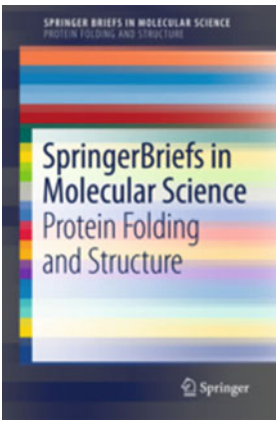

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Cláudio M. Gomes is Associate Professor with habilitation at the Faculty of Sciences University of Lisboa where he heads the Protein Folding and Misfolding Laboratory as part of BioISI Biosystems and Integrative Sciences Institute. He obtained is PhD in Biochemistry (1999) from the Universidade Nova de Lisboa, as a graduate of the Gulbenkian Ph.D. program in Biology and Medicine, and holds Habilitation (Agregação) in Biochemistry (2013). He has extensive publishing and editorial activities, both as a prolific author, member of Editorial boards and editor of thematic issues and books. In collaboration with Springer, he set the Springer Briefs subseries on Protein Folding and Structure, which launched its first volume in 2014.

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Carlos M. Farinha

CFTR and Cystic Fibrosis

From Structure to Function

Springer

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Foreword

Protein function is tightly related to folding and structure, but proteins in the cell also need to be at the right location to carry out their biological roles. Therefore, as a protein folds, complex machineries assure, in tightly orchestrated processes, not only the quality of folded proteins but also its correct cellular trafficking and lipid bilayer insertion in the case of membrane proteins. Indeed, several human diseases result from combined folding and trafficking defects. Among these is cystic fibrosis, a hallmark loss of function protein-folding disease caused by defects in a transmembrane chloride channel called cystic fibrosis transmembrane conductance regulator (CFTR). CFTR misfolding in cystic fibrosis, which results mostly from the F508del mutation, impairs traffic and membrane insertion causing proteasomal degradation. In this fifth volume of the "Protein Folding and Structure" series of the "Springer Briefs in Molecular Science", the leading expert Carlos M. Farinha provides an updated perspective of the genetic, functional and cellular processes involving CFTR in connection with cystic fibrosis. Starting with a historical perspective on cystic fibrosis and its clinical features, the author departs into an in-depth description of the biology of the CFTR protein, ending with a discussion on the latest approaches aimed at developing corrective therapies for cystic fibrosis. Through this integrated perspective, the reader will obtain a unique insight into this fascinating membrane-bound protein and its associated disease. Enjoy reading.

Lisboa
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Cláudio M. Gomes
Editor
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Carlos M. Farinha obtained his Ph.D. (2003) and Habilitation (2015) in Biochemistry from the University of Lisbon. He has worked at the National Institute of Health Dr. Ricardo Jorge and at the Faculty of Sciences, University of Lisbon with training periods at the Johns Hopkins University School of Medicine, Baltimore, MD, USA and at the University of Pittsburgh School of Medicine—Children's Hospital of Pittsburgh, Pittsburgh, PA, USA. Currently, he is Assistant Professor with habilitation at the Faculty of Sciences, University of Lisbon, and Principal Investigator at BioISI—Biosystems and Integrative Sciences Institute. His research focuses on the molecular mechanisms of cystic fibrosis (CF), in particular the endoplasmic reticulum retention and early degradation of CFTR's most common mutant and characterization of the role of CFTR interacting proteins. He received the 2012 ERS Romain Pauwels Research Award from the European Respiratory Society for "research into the different aspects of CFTR biology".

Abbreviations

Aa	Amino acid
ABC	ATP-binding cassette
AFT	Arginine-framed tripeptide
ASL	Airway surface liquid
ATP	Adenosine 5'Triphosphate
Bag	Bcl-2 associated atharogene
Ca^{2+}	Calcium ion
CaCC	Calcium-activated Chloride Channel
CAL	CFTR-associated ligand
cAMP	Cyclic Adenosine 5'Monophosphate
CBAVD	Congenital bilateral absence of the vas deferens
CF	Cystic fibrosis
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator
CFTR	Gene encoding CFTR
CHIP	Carboxy-terminal of Hsp70 interacting protein
CK2	Casein kinase 2
Cl^-	Chloride ion
COP	Coat protein
Dab-2	Disabled-2
DHS	DNase I hypersensitive site
ECL	Extracellular loop
EMT	Epithelial-to-mesenchymal transition
ENaC	Epithelium Sodium Channel
EPAC	Exchange protein directly activated by cAMP
ERAD	Endoplasmic reticulum-associated degradation
ER	Endoplasmic reticulum
ERQC	Endoplasmic reticulum quality control
FDA	Food and Drug Administration
GERAD	Glycoprotein endoplasmic reticulum associated degradation

GSH	Glutathione
H^+	Hydrogen ion
HCO_3^-	Bicarbonate
Hdj	Human DnaJ
HGF	Hepatocyte growth factor
Hsp	Heat shock protein
HTS	High Throughput Screening
IBMX	3-isobutyl-1-methylxanthine
ICL	Intracellular loop
K^+	Potassium ion
LMTK2	Lemur tyrosine kinase 2
MDR	Multidrug resistance
MRP	Multidrug-related protein
MSD	Membrane-spanning domain
Na^+	Sodium ion
NBD	Nucleotide binding domain
NH3	Na^+/H^+ exchanger
NHERF1	Na^+/H^+ exchanger regulatory factor isoform-1
NKCC1	Na^+-K^+-$2Cl^-$ cotransporter
NMD	Nonsense-mediated decay
NPD	Nasal Potential Difference
ORCC	Outwardly Rectifying Chloride Channel
PCR	Polymerase chain reaction
PDE	Phosphodiesterases
PDZ	Psd-95, Disc-large and ZO-1
PGE	Prostaglandins
PI	Pancreatic Insufficiency
PK	Protein kinase
PPQC	Peripheral protein quality control
PS	Pancreatic Sufficiency
PTC	Premature termination codon
RD	Regulatory domain
RFLP	Restriction fragment length polymorphism
ROMK	Renal outer medullary K^+ channel
SLC26	Solute carrier 26 family
SNARE	Soluble NSF Attachment Protein Receptor
SRP	Signal recognition particle
SUMO	Small ubiquitin-like modifier
SYK	Spleen tyrosine kinase
TAP	Transporter associated with antigen presentation
TfR	Transferrin
TM	Transmembrane segment
Ubc	Ubiquitin-conjugating enzymes

UGGT	UDP-glucose glucosyltransferase
UPP	Ubiquitin Proteasome Pathway
WNK	With-no-lysine kinase
wt-CFTR	Wild-type CFTR

Abstract

Cystic fibrosis (CF) is a monogenic autosomal recessive disorder that affects Caucasian individuals. Clinically it is characterized by chronic pulmonary dysfunction, pancreatic insufficiency, increased saline concentration in sweat, and male infertility. The gene responsible for the disease was cloned in 1989 and encodes an ABC transporter, the 1480-amino acid protein named Cystic Fibrosis Transmembrane Conductance Regulator (CFTR), that functions as a chloride (Cl^-) channel in the apical membrane of epithelial cells.

Since the cloning of the gene over 2,000 mutations were identified but a single one, deletion of phenylalanine 508 (F508del), accounts for about 70% of the CF chromosomes.

CFTR protein is synthesized at ER-anchored ribosomes and co-translationally inserted into the ER membrane where it is core-glycosylated. From there, the protein is exported to the Golgi where it undergoes several modifications at its glycidic moieties and after full processing finally it reaches the plasma membrane. This process is complex and a certain proportion of the wt protein and almost all the protein bearing the F508del mutation fail this export, being alternatively sent to proteasomal degradation coupled to the ER.

This brief focus on CFTR and Cystic Fibrosis, as a paradigmatic example of a loss-of-function conformational disorder, and is directed to a targeted audience whose interests span from human genetics to protein folding, protein trafficking, and physiology.

It covers the basic aspects of Cystic Fibrosis as a disorder, focusing on its genetics and mutation prevalence/incidence. Then, the major part is devoted to the CFTR protein—its structure and classification within the ABC transporter superfamily, its biogenesis with membrane insertion and chaperone-assisted folding, its glycosylation and the endoplasmic reticulum quality control mechanisms that assess CFTR folding status. Then, attention is given to post-ER trafficking and regulation

of membrane stability/anchoring and to CFTR function. This is linked to the molecular mechanisms through which different CFTR mutations cause cystic fibrosis.

The last part covers the different efforts aiming at rescuing the basic defect, most of which address CFTR dysfunction(s).

Keywords CFTR · Cystic Fibrosis · Protein folding · Protein trafficking · Ion channels · Membrane proteins · ABC transporters · Post-translational modifications