




PNH and the GPI-Linked Proteins

Edited by Neal S. Young *and* Joel Moss




Paroxysmal Nocturnal
Hemoglobinuria and the
Glycosylphosphatidylinositol-Linked
Proteins

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Paroxysmal Nocturnal Hemoglobinuria and the Glycosylphosphatidylinositol- Linked Proteins



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Contents

Contributors **xi**

Preface **xiii**

1

A Brief History of PNH

Wendell Rosse

The Diagnosis of PNH **8**

Summary **15**

References **16**

2

Genetics of PNH

Lucio Luzzatto and Khédoudja Nafa

Biochemical Genetics of PNH in Somatic Cells **21**

The *PIG-A* Gene **23**

The PIG-A Protein	24
Detecting Mutations in the <i>PIG-A</i> Gene	27
Germ Line <i>PIG-A</i> Mutations	32
The Spectrum of Somatic Mutations in the <i>PIG-A</i> Gene	33
<i>PIG-A</i> Mutations without PNH	40
Structure–Function Relationships	41
Correlation between Phenotypes and Genotypes	42
Comparison of the Spectrum of Mutations in Three X-Linked Genes: <i>PIG-A</i> , <i>FVIII</i> , and <i>G6PD</i>	42
Conclusion	43
References	44

3

Hemolysis in PNH

Charles J. Parker

Introduction	49
The Classical Pathway of Complement	55
The Alternative Pathway of Complement	61
Phenotypic Mosaicism	64
Functional Basis of the Abnormal Sensitivity of the Erythrocytes of PNH to Complement-Mediated Lysis	68
Treatment of Hemolysis	83
Summary and Conclusions	86
References	89

4

Thrombotic Complications in PNH

Elaine M. Sloand and Neal S. Young

Introduction	101
Incidence of Thrombosis in PNH	102
Factors Associated with Venous Thrombosis	103
Platelet Abnormalities in PNH	104
Role of Red Cell and Platelet Microvesicles	107
Urokinase Activator Receptor (uPAR) and Cell-Mediated Fibrinolysis	108

Treatment of Thrombosis in PNH	109
Summary	109
References	110

5

Bone Marrow Failure in PNH

Daniel E. Dunn, Johnson M. Liu, and Neal S. Young

Introduction	113
Pathophysiology of Marrow Failure in PNH	115
An Immune Model of PNH Pathogenesis	120
Clinical Course and Treatment of Marrow Failure in PNH	127
Summary	130
References	131

6

Animal Models of PNH

Taroh Kinoshita, Monica Bessler, and Junji Takeda

Introduction	139
Mouse <i>Piga</i> Gene	141
<i>In Vitro</i> Differentiation of PIGA(–) ES Cells	143
Chimeric Mice Bearing PIGA(–) Hematopoietic Stem Cells	149
Hematopoiesis by Cells from Patients with PNH in SCID Mice	154
Conclusions and Perspectives	155
References	155

7

The Function of GPI-Anchored Proteins

Ian Okazaki and Joel Moss

Introduction	159
GPI-Linked Proteins and Cell Signaling	161

Role of GPI-Anchored Proteins in Insulin Action	166
GPI-Anchored Proteins Function as Receptors	166
GPI Anchors and Membrane Structure	168
Summary	170
References	171

8

GPI in Lower Animals

Louis Schofield

Introduction	179
Structures of Protozoal GPIs	180
Evidence for GPI-Mediated Signaling in Mammalian Cell Biology	182
Signal Transduction in Host Cells by Protozoal GPIs	185
Parasite GPIs as Functional Toxins and Pathogenicity Factors	187
Regulation of Macrophage Function by Glycoconjugates of <i>Leishmania</i>	188
Regulation of Host Cells by Ceramide-Containing GPIs of <i>T. cruzi</i>	189
Insulin-Mimetic Activities of Protozoal GPIs	189
CD1d-Restricted NK T Cells and Immunity to GPI-Anchored Proteins	190
Conclusions	191
References	192

9

Synthesis of the GPI Anchor

Daniel Seivlever, Rui Chen, and M. Edward Medof

Introduction	199
GPI Biosynthetic Pathway	200
Mammalian and Yeast GPI-Anchor Defective Mutants	203
GPI-Anchor Addition to Proteins	207
Biological Implications of GPI Anchoring	210
Conclusions	213
References	214

10

Functional and Structural Organization of GPI-Anchored Proteins in Cellular Membranes

Satyajit Mayor

Introduction	221
GPI-Anchor Function and the "Raft" Hypothesis	221
Lateral Heterogeneity in Cell Membranes	222
Detergent-Resistant Membranes and Their Connection with Rafts	223
Evidence for Rafts in Living Cell Membranes	227
Involvement of Rafts in Biosynthetic and Endocytic Sorting	230
Rafts and Signaling by GPIAPs	232
In Conclusion	233
References	233

11

Structure and Function of GPI-Specific Phospholipases

Martin G. Low

Introduction: GPI Anchors and Phospholipases	239
Biochemical Properties of Plasma GPI-PLD	245
Distribution of GPI-PLD in Tissues and Cells	252
Physiological Role of GPI-PLD	257
References	262

<i>Appendix: Sequence of the Coding Region of the Human PIG-A Gene</i>	269
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<i>Index</i>	271
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Preface

Paroxysmal Nocturnal Hemoglobinuria and the Glycosylphosphatidylinositol-Linked Proteins reflects the recent fortunate coincidence of breakthroughs in basic science laboratories that impact our understanding of disease and of insights derived from the study of human illness that inspire such experiments.

This book critically reviews the clinical character and underlying biology of paroxysmal nocturnal hemoglobinuria (PNH). Early studies of trypanosomes, a parasitic scourge of humans, led to the discovery of the glycosylphosphatidylinositol (GPI) anchor and eventually to the association of the red cell defect in PNH patients with the mammalian family of GPI-linked proteins. The recognition of a deficiency in a distinctive class of cell-surface proteins and of a single acquired genetic defect in hematopoietic stem cells has allowed definition of the genetic and biochemical nature of this strange disease. After more than a century of observation and study, we now understand how severe red blood cell destruction, life-threatening thrombosis, and aplastic anemia can be combined in a single patient, and the specific lesion responsible for intravascular hemolysis has been defined. But many provocative questions still remain, ranging from the physiologic roles of GPI-anchored proteins and membrane rafts in the cell to the relationship between a protein defect and profound marrow failure.

The authors of this volume are major investigators in biochemistry, molecular biology, and clinical medicine. As editors, we are especially appreciative of their willingness to prepare original syntheses for this monograph, and we hope that the readers will be educated and stimulated by their contributions.

Neal S. Young
Joel Moss

A Brief History of PNH

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Paroxysmal nocturnal hemoglobinuria (PNH) was one of the first discrete hematological entities to be described, undoubtedly due to the dramatic content of its primary symptom—hemoglobinuria. The passage of red, dark brown, purple, or black urine is readily noted by the patient and induces a distinct impression on the physician.

The Hippocratean writings contain numerous allusions to “black urine” and scholars have debated whether they are describing blood or hemoglobin in the urine or simply concentrated urine, because most of the patients were moribund and most likely poorly hydrated. One word used (*μελανα*) means specifically black or very dark, while another (*παχυσ*, which has the general meaning “thick”) is used to describe “concocted” urine. The latter is clearly concentrated urine of the dehydrated (a not infrequent condition in Hippocrates’ case reports), leaving some doubt of the meaning of the former. However, a nocturnal or morning pattern of dark urine is not described, leading to the conclusion that Hippocrates probably is describing hemoglobinuria from malaria (many of the patients were febrile) or from some other cause other than PNH.

In the Middle Ages, up to about the 17th century, close observation of the urine was a primary diagnostic test of the patient’s condition; textbooks detail what should be observed and the presumed causes for the changes seen. (Treatises on distinguishing horse urine from human urine were published because apparently the expertise of the physician was tested by substituting it for the urine of the patient.) Although dark black and red urine are described, the nightly pattern of PNH is not.

The first case report which might be of a patient with PNH was that by Charles Stewart, a Scottish surgeon practicing in Archangel, the northernmost