Helmut Popper

Pathology of Lung Disease

Morphology – Pathogenesis – Etiology

Springer

Pathology of Lung Disease

Helmut Popper

Pathology of Lung Disease

Morphology – Pathogenesis – Etiology

With contribution by Prof. Fiorella Calabrese

Springer

Helmut Popper
Institute of Pathology
Medical University Graz
Graz
Austria

ISBN 978-3-662-50489-5 ISBN 978-3-662-50491-8 (eBook)
DOI 10.1007/978-3-662-50491-8

Library of Congress Control Number: 2016948439

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer-Verlag GmbH Germany
The registered company address is Heidelberger Platz 3, 14197 Berlin, Germany

Preface

Scio, me nihil scire (a phrase attributed to the Greek philosopher Socrates)

As an academic pathologist, I see this phrase not as discouraging but instead encouraging. In almost every disease, there are many unanswered questions, so when our students ask about it, we have to answer that we do not know. But many of the "I do not know answers" can be the starting point for a new research proposal – in this sense I mean our missing knowledge "is not discouraging" at all.

Pathology has reached an important crossroad: there is danger of losing competence on one hand but also a bright revival of the importance of pathology. Many new discoveries have shed light into pathogenesis, which we had previously simply described from our understanding of morphology, but which now we can interpret with a completely different perspective of understanding underlying molecular processes.

In tumors, we have learned a lot about the importance of genetic abnormalities and what the results from these alterations are. We are just learning to separate driver mutations and alterations of genes from cooperating mutations and use some of these genetic abnormalities to treat our patients in a completely new way with fewer side effects.

In inflammatory and immune diseases, we have learned that lymphocytes can act in an opposite way, either bringing good or bad actions in a given disease. Lymphocytes can aggravate the damage of lesions initiated by infectious organisms or help to defend against the organisms. Developments in immunology research have broadened our understanding of regulations between the many types of regulatory lymphocytes and antigen-presenting cells. This will not only enable us to more precisely diagnose immune diseases but also to promote immune attack toward tumor cells in patients. In addition, immunooncology has entered tumor therapy, and pathologists are faced with new challenges in the interpretation of anti- or pro-tumor action of the patient's immune system.

Has this changed our recognition? If you do an Internet research looking for basic science investigations, pathologists are hardly in the forefront of this type of research; they are rarely leading. Most often, if ever they are coauthors, because they have contributed some tissues for the investigation, or sometimes have made the diagnosis, so the research material could be grouped.

And many pathologists are just happy to contribute on this small scale. Some are even happy to outsource molecular pathologic diagnostics to private companies instead of doing this investigation "in-house." Other pathologists have developed a pseudoscientific habit: By changing classifications every 4–5 years, they assume they will be regarded as important. But this old style of changing little diagnostic boxes and giving them new names, without creating new information, will not last for more than a few years. Will this increase our reputation? I think not. This behavior will finally degrade pathology departments into a tissue repository, and pathologists into biobank curators, who do not care what this tissue is used for.

Is there an alternative? Where is the bright light and future?

We need to learn the biology of the diseases, and we need to familiarize with their genetic abnormalities and what impact genetic changes might have. In our daily practice, we often see a time sequence of pathogenetic events in a given disease. We need to assemble these single-time events like pictures into a movie (early–intermediate–late, resolving–recurrent). For example, early on, hyperplasia might be the first step into neoplasia. The cells acquire better access to nutrition and oxygen supply, which enables them to grow faster and outrange their normal neighbors. Some of these cells develop atypia; among them are tissue stem cells, which can move out, settle down at another focus, and establish another hyperplastic focus. Some of these colonies will develop into preneoplastic lesions, others will be whipped out by the immune system, and others will die due to defective DNA repair and apoptosis. All these events will leave footprints in the tissue, and we as pathologists should read and interpret these footprints and correlate this with the underlying genetic changes: phenotypic genotypic correlation is a key to better understanding and better diagnostics. The same is true for immune diseases. Understanding the interaction of immune cells in an autoimmune disease and analyzing the cells present at a given time sequence might not only provide a more accurate diagnosis but also might provide understanding of the disease progression and finally pave ways for better treatment. So a successful new type of pathologist will understand the biology behind a given morphology and in this way will be a welcomed partner in research as well as in the patient management team.

It will be impossible to describe all aspects of etiology and pathogenesis in all diseases we will cover; this would go beyond the scope of this book on lung diseases. However, I will summarize as good as possible pathogenesis and etiology in each of the entities, being aware that I am not able to give a complete overview.

This book is based on my experience of dealing with lung diseases for more than 35 years. I present a one-author book instead of the common multiauthor books, because all the chapters will be in line with my perspective of interpreting pathology. And this can be summarized as follows: pattern recognition is a first step of analysis, but looking into the pathogenesis and etiology of a disease is what makes a good pathologist. One chapter is an exception: My practice in transplant pathology is limited. In Austria, lung transplantation is concentrated in Vienna, which results to less tissues being studied. So I was happy that Fiorella was willing to contribute this chapter.

I encourage you as the reader and user of this book to communicate with me on your critiques, as this is important for future improvements. I have learned more from mistakes than from everything else. Misdiagnosis was my best teacher. As in every scientific discipline, mistakes and misinterpretations do occur, sometimes simply overlooked.

Graz, Austria Helmut Popper

Acknowledgments

I am indebted to my family especially to my wife Ursula for her understanding during my increasing commitment with lung pathology.

I am also grateful to my teachers Helmut Denk, Liselotte Hochholzer (AFIP), and Hans Becker for their encouragement to study lung pathology in depth and promoting me to go abroad to learn new technologies and learn new ways of interpreting lung tissue reactions. I would also like to thank numerous colleagues with whom I shared my enthusiasm and time to discuss lung pathology during international conferences. Many of them became friends during the process to form the European Working Group on Pulmonary Pathology. It would be impossible to name them all personally.

Contents

1 Development of the Lung 1
1.1 Genetic Control of the Development 4
1.2 Comparison of Lung Development Across Species 4
References 4

2 Normal Lung 7
2.1 Gross Morphology 7
2.2 The Airways 9
2.3 Lymphoreticular Tissue and the Immune System of the Lung 18
2.4 Comparison of Human Lung to Other Species 18
References 19

3 Pediatric Diseases 21
3.1 Developmental and Inherited Lung Diseases 21
3.1.1 Aplasia and Acinar/Alveolar Dysgenesis 21
3.1.2 Growth Retardation 24
3.1.3 Vascular Malformations 24
3.1.4 Malformations of the Airway System 33
3.1.5 Lung Pathology in Chromosomal Abnormalities 41
3.1.6 Inborn Errors of Metabolism 42
3.1.7 Cystic Fibrosis 47
3.1.8 Neuroendocrine Cell Hyperplasia of Infancy (NEHI) . . 48
3.2 Pneumonia in Childhood Including Noninfectious Interstitial Pneumonias 50
3.2.1 Chronic Pneumonia of Infancy (CPI) 50
3.2.2 Mendelson Syndrome in Children and Silent Nocturnal Aspiration 51
References 53

4 Edema 59
4.1 Gross Morphology 59
4.2 Histology 59
4.3 High-Altitude Edema (HAPE) 59
References 61

5 Air Filling Diseases 63
5.1 Atelectasis 63
5.1.1 Gross Morphology 64
5.1.2 Histology 64
5.2 Emphysema 65
5.2.1 Gross Morphology 65
5.2.2 Histology 66
5.3 Emphysema and Lung Function 72
5.3.1 Factors Contributing to Emphysema Development 73
References 74

6 Airway Diseases 77
6.1 Tracheitis and Bronchitis 77
6.1.1 Gross Morphology 77
6.1.2 Histology 78
6.2 Bronchial Asthma 80
6.2.1 Etiology 80
6.2.2 Immune Mechanisms 80
6.2.3 Gross Morphology 82
6.2.4 Histology 82
6.3 Bronchiolitis 84
6.4 The Classification 84
References 100

7 Smoking-Related Lung Diseases 103
7.1 Langerhans Cell Histiocytosis 103
7.1.1 Histology 103
7.1.2 Molecular Biology 104
7.1.3 Function of LH Cells 106
7.1.4 Differential Diagnosis 106
7.2 Respiratory Bronchiolitis: Interstitial Lung Disease (RBILD) 106
7.2.1 Histology 107
7.3 Desquamative Interstitial Pneumonia (DIP) 109
7.3.1 Histology 111
7.4 Smoking-Induced Interstitial Fibrosis (SRIF)/Respiratory Bronchiolitis-Associated Interstitial Lung Disease (RBILD) 112
7.5 Chronic Obstructive Pulmonary Disease (COPD) 113
7.5.1 What Are the Mechanisms? Why Not Every Smoker Develops COPD? 114
References 116

8 Pneumonia 121
8.1 Alveolar Pneumonias (Lobar and Bronchopneumonia) 121
8.1.1 Clinical Symptoms of Pneumonias 123
8.1.2 Alveolar Pneumonias (Bronchopneumonia and Lobar Pneumonia; Adult and Childhood) 123

8.1.3 Diffuse Alveolar Damage (DAD) and Acute Interstitial Pneumonia 126
8.1.4 Lymphocytic Interstitial Pneumonia (LIP) 131
8.1.5 Giant Cell Interstitial Pneumonia (GIP; See Also Under Pneumoconiosis) 133
8.1.6 The Infectious Organisms 133
8.1.7 Bronchopulmonary Dysplasia (BPD) 142
8.1.8 Aspiration Pneumonia 142
8.1.9 HIV Infection 142
8.2 Granulomatous Pneumonias 144
8.2.1 Introduction 144
8.2.2 What Influences Granuloma Formation? Why Necrosis? 144
8.2.3 Morphologic Spectrum of Epithelioid Cell Granulomas 146
8.2.4 The Causes of Epithelioid Cell Granulomas and Their Differential Diagnosis 147
8.2.5 Methods to Be Used for a Definite Diagnosis of Infectious Organisms 170
8.3 Fibrosing Pneumonias (Interstitial Pneumonias) 173
8.3.1 Historical Remarks on Interstitial Pneumonia Classification 173
8.3.2 Usual Interstitial Pneumonia (UIP)/Idiopathic Pulmonary Fibrosis (IPF) 174
8.3.3 Familial IPF (FIPF) 182
8.3.4 Nonspecific Interstitial Pneumonia (NSIP) 184
8.3.5 Organizing and Cryptogenic Organizing Pneumonia (OP, COP) 187
8.3.6 Airway-Centered Interstitial Fibrosis (ACIF) 189
References 191

9 Immunological Lung Diseases 199
9.1 Introduction into Interstitial Lung Diseases 199
9.2 Autoimmune Diseases 200
9.2.1 Rheumatoid Lung Disease 200
9.2.2 Systemic Lupus Erythematosus 207
9.2.3 Systemic Sclerosis 211
9.2.4 Dermatomyositis/Polyserositis 215
9.2.5 Sjøgren's Syndrome 217
9.2.6 Mixed Collagen Vascular Diseases (CVD) 220
9.2.7 Goodpasture Syndrome 221
9.2.8 Other Autoimmune Diseases Affecting the Lung 223
9.2.9 Surfactant-Related Interstitial Pneumonias: Alveolar Proteinosis 225
9.3 Diseases of the Innate Immune System Based in Genetic Abnormalities 226
9.3.1 Idiopathic Pulmonary Hemosiderosis 226
9.3.2 Lymphangioleiomyomatosis (LAM) 227

9.3.3 Hermansky-Pudlak Syndrome 232
9.3.4 Erdheim-Chester Disease 234
9.4 Allergic Diseases 234
9.4.1 Allergic Bronchopulmonary Mycosis 234
9.5 Drug Allergy 234
References 236

10 Eosinophilic Lung Diseases 239
10.1 Introduction 239
10.2 Allergic or Hyperreactive Diseases 239
10.2.1 Allergic Bronchopulmonary Mycosis (Aspergillosis) 239
10.3 Eosinophilic Pneumonias (EP) 241
10.3.1 Epidemiology and Incidence 241
10.3.2 Clinical Presentation and CT 241
10.3.3 Pathogenesis and Etiology 242
10.3.4 Immunohistochemistry, Genetics, and Immunology 247
References 248

11 Vascular Lung Diseases 251
11.1 Infarct and Thromboembolic Disease 251
11.1.1 Gross Examination and Histology 251
11.2 Vasculitis 251
11.2.1 Classification of Vasculitis 251
11.2.2 Granulomatosis with Polyangiitis 253
11.2.3 Eosinophilic Granulomatosis with Polyangiitis (EGPA, Formerly Called Churg-Strauss Vasculitis) 255
11.2.4 Microscopic Polyangiitis 256
11.2.5 Panarteritis Nodosa 258
11.3 Secondary Vasculitis with Infection 260
11.4 Secondary Vasculitis Without Infection 261
11.5 Vascular Diseases and Malformation 262
11.5.1 Histology 262
11.6 Malformation and Systemic (Inborn) Vascular Diseases in Children 263
11.7 Pulmonary Hypertension 263
11.7.1 Mechanisms of PAH 269
11.8 Alveolar Hemorrhage 270
11.9 Diseases of the Lymphatics (Adult and Childhood) 270
11.10 Malformation 270
11.11 Obstruction 271
11.12 Inflammation 271
References 272

12 Metabolic Lung Diseases 275
12.1 Amyloidosis 275
12.2 Disturbed Calcium Metabolism 277
12.3 Lipid and Surfactant Metabolism 282
12.4 Iron and Elastin Metabolism 288
References 289

13 Pneumoconiosis and Environmentally Induced Lung Diseases 291
13.1 Introduction 291
13.2 Silicosis 292
13.3 Silicatosis 294
13.3.1 Asbestosis 295
13.3.2 Other Silicatoses 296
13.4 Metal-Induced Pneumoconiosis and Disease 300
13.4.1 Hard Metal Lung Disease 302
13.4.2 Aluminosis 302
13.4.3 Chromium and Vanadium 305
13.4.4 Tungsten 305
13.4.5 Cobalt 306
13.4.6 Other Metals 307
13.4.7 Mercury 308
13.4.8 Nickel 308
13.4.9 Arsenic, Tin 308
13.4.10 Indium, Tin 308
13.4.11 Siderosis 309
13.4.12 Rare Metals and Chronic Allergic Metal Diseases . . 309
13.5 Cotton Dust, Flock Workers' Lung, and Byssinosis 312
13.6 Manmade Fibers, Hydrocarbon Compounds, and Polyvinyls 312
13.7 Pesticides and Insecticides 312
13.8 Inhalation of Combustibles 313
13.9 Cocaine and Marijuana 313
References 315

14 Iatrogenic Lung Diseases 321
14.1 Drug-Induced Interstitial Lung Diseases 321
14.2 Action of Drugs and Morphologic Changes Associated with Drug Metabolism 321
14.2.1 Granulomatous Reactions 323
14.2.2 DAD Pattern 323
14.2.3 Organizing Pneumonia Pattern 323
14.2.4 NSIP and LIP Patterns 323
14.2.5 UIP Pattern 323
14.2.6 Vasculitis 328
14.2.7 Edema 328
14.2.8 Fibrinous Pneumonia 328

14.3 Iatrogenic Pathology by Radiation 328
References 329

15 Bronchoalveolar Lavage as a Diagnostic and Research Tool 331
15.1 Where and When Doing BAL? 331
15.2 Processing of BAL 332
References 334

16 Lung Transplantation-Related Pathology 335
16.1 Explant Pathology 335
16.1.1 Obstructive Diseases 335
16.1.2 Restrictive Diseases 336
16.1.3 Vascular Disease (Pulmonary Hypertension) 338
16.2 Perioperative Complications 338
16.3 Lung Allograft Rejection 339
16.3.1 Hyperacute Lung Rejection 339
16.3.2 Acute Rejection (Grade A, B) 339
16.3.3 Chronic Rejection (Grade C and D) 339
16.3.4 Emerging Immunological Lesions 342
16.4 Infections 344
16.4.1 Viral Infection 344
16.4.2 Bacterial Infection 345
16.4.3 Fungal Infections 345
16.5 Tumors 346
16.5.1 Other Tumors 346
16.6 Other Complications 347
16.6.1 Graft-Versus-Host Disease (GVHD) 347
16.6.2 Disease Recurrence in the Graft 347
16.6.3 Drug Injury 347
References 347

17 Lung Tumors 353
17.1 Epithelial Tumors 353
17.1.1 Benign Epithelial Tumors 353
17.2 In Situ Carcinoma and Precursor Lesions 382
17.2.1 Preneoplastic Lesions – Squamous Cell Dysplasia . . 382
17.2.2 Atypical Adenomatous Hyperplasia 385
17.2.3 Bronchiolar Columnar Cell Dysplasia 385
17.2.4 Atypical Goblet Cell Hyperplasia 388
17.2.5 Neuroendocrine Cell Hyperplasia 388
17.3 Malignant Epithelial Tumors 392
17.3.1 Epidemiology 392
17.3.2 Carcinogenesis: Our Current Sight on the Development of Cancer 393
17.3.3 Common Carcinomas 398
17.3.4 Carcinomas with Clear Cells 448
17.3.5 Rhabdoid Carcinoma 449
17.3.6 LC of Hepatoid Phenotype 449
17.3.7 Lymphoepithelioma-like Carcinoma 449

17.3.8 Adenosquamous Carcinoma. 452
17.3.9 Diagnosis on Small Biopsies and Cytology Preparations 452
17.3.10 Salivary Gland-Type Carcinomas 454
17.3.11 The Sarcomatoid Carcinomas 461
17.3.12 Primary Intrapulmonary Germ Cell Neoplasms 465
17.3.13 NUT Carcinoma. 469
17.3.14 Staging of Pulmonary Carcinomas 470
17.4 Benign and Malignant Mesenchymal Tumors. 470
17.4.1 Hamartoma. 470
17.4.2 Smooth Muscle Tumors 471
17.4.3 Fibromatous Tumors 480
17.4.4 PEComa (Clear Cell Tumor and Sugar Tumor) 491
17.4.5 Chondroma, Osteoma, and Lipoma 493
17.4.6 Tumors with Nervous Differentiation 494
17.4.7 Triton Tumor 499
17.4.8 Paraganglioma 500
17.4.9 Pulmonary Meningioma. 502
17.4.10 Vascular Tumors. 503
17.4.11 Primary Melanoma of the Bronchus 524
17.5 Hematologic Tumors Primarily Arising in the Lung. 527
17.5.1 Lymphomas 527
17.5.2 Dendritic Cell and Histiocytic Tumors 535
17.6 Childhood Tumors. 542
17.6.1 Congenital Peribronchial Myofibroblastic Tumor . . . 542
17.6.2 Fetal Lung Interstitial Tumor (FLIT). 547
17.6.3 Pleuropulmonary Blastoma 547
17.6.4 Adenocarcinoma of the Lung Arising in CPAM 551
17.6.5 Squamous Cell Papilloma and Papillomatosis. 552
17.6.6 Capillary Hemangiomatosis. 553
References. 553

18 Metastasis. 577
18.1 Tumor Establishment and Cell Migration. 577
18.1.1 Angiogenesis, Hypoxia, and Stroma (Microenvironment). 577
18.1.2 The Role of Hypoxia in Tumor Cell Migration and Metastasis 579
18.1.3 Escaping Immune Cell Attack 582
18.1.4 Migration 582
18.2 Vascular Invasion: Lymphatic/Hematologic 586
18.2.1 Blood Vessels 586
18.2.2 Lymphatic Vessels 587
18.3 Extravasation. 587
18.4 Preparing the Distant Metastatic Focus 588
18.4.1 Angiogenesis 589
18.5 Metastasis 589
18.5.1 Brain Metastasis. 590
18.5.2 Lung Metastasis 593
18.5.3 Bone Metastasis 593

18.5.4 Pleural Metastasis 594
18.5.5 Lymph Node Metastasis. 595
18.6 Metastasis to the Lung 596
References. 605

19 Molecular Pathology of Lung Tumors 611
19.1 Introduction. 611
19.2 Therapy Relevant Molecular Changes in Pulmonary Carcinomas 611
19.2.1 NSCLC and Angiogenesis 611
19.2.2 NSCLC and Cisplatin Drugs: The Effect of Antiapoptotic Signaling 612
19.2.3 Thymidylate Synthase Blocker 612
19.2.4 Receptor Tyrosine Kinases in Lung Carcinomas 613
19.2.5 TP53: The Tumor Suppressor Gene. 613
19.3 Adenocarcinomas 613
19.3.1 EGFR 614
19.3.2 KRAS. 614
19.3.3 EML4ALK1 and Additional Fusion Partners 615
19.3.4 ROS1 615
19.3.5 KIF5B and RET 616
19.3.6 MET 616
19.3.7 Others Genes 616
19.4 Squamous Cell Carcinomas 617
19.4.1 FGFR1 617
19.4.2 DDR2 and FGFR2 617
19.4.3 SOX2 Amplification. 617
19.4.4 PTEN Mutation-Deletion. 618
19.4.5 PDGFRA Amplification. 618
19.4.6 CDKN2A (p16) Mutation, Deletion, and Methylation 618
19.4.7 Notch1 Mutation 618
19.4.8 REL Amplification 618
19.5 Large Cell Carcinoma 618
19.6 Other Types of Large Cell Carcinomas. 619
19.7 The Neuroendocrine Carcinomas 619
19.7.1 Small Cell Neuroendocrine Carcinoma 619
19.7.2 Large Cell Neuroendocrine Carcinoma 620
19.7.3 Carcinoids 620
19.8 Salivary Gland Type Carcinomas 621
19.8.1 Mucoepidermoid Carcinoma 621
19.8.2 Adenoid Cystic Carcinoma 621
19.9 Sarcomatoid Carcinomas (SC) 622
19.10 Preneoplastic Lesions 622
19.10.1 Hyperplasia of Goblet Cells and Squamous Metaplasia/Dysplasia 623
19.10.2 Genetic Aberrations in AAH 623
19.10.3 Neuroendocrine Cell Hyperplasia 624

19.11 Selected Examples of Benign and Mesenchymal Lung Tumors . . . 624
19.11.1 Benign Epithelial Tumors . . . 624
19.11.2 Sclerosing Pneumocytoma . . . 624
19.12 Tumors Induced by Mutations of the TSC Genes (Related to Tuberous Sclerosis) . . . 625
19.12.1 Multifocal Nodular Pneumocyte Hyperplasia (MNPH) . . . 625
19.12.2 Lymphangioleiomyomatosis (LAM) . . . 625
19.12.3 Clear Cell Tumor (Sugar Tumor, PEComa = Perivascular Epithelioid Cell Tumor) . . . 625
19.13 Malignant Tumors of Childhood . . . 626
19.13.1 Pleuropulmonary Blastoma . . . 626
19.13.2 Congenital Myofibroblastic Tumor . . . 626
19.14 Final Remarks . . . 626
References . . . 626

20 Immunotherapy of Lung Tumors . . . 639
20.1 Systems Known to Be Able to Induce Immune Tolerance Toward Foreign Antigens . . . 640
References . . . 642

21 Diseases of the Pleura . . . 645
21.1 Hemorrhage . . . 645
21.2 Effusion . . . 645
21.3 Inflammation: Pleuritis . . . 645
21.3.1 Purulent Pleuritis . . . 645
21.3.2 Hemorrhagic Pleuritis . . . 646
21.3.3 Chronic Pleuritis . . . 646
21.4 Tumors . . . 646
21.4.1 Mesothelioma . . . 649
21.4.2 Multicystic Mesothelioma . . . 662
21.4.3 Adenomatoid Tumor . . . 663
21.4.4 Solitary Fibrous Tumor of the Pleura (Fibroma, SFT) . . . 663
21.4.5 Desmoid Tumor . . . 665
21.4.6 Calcifying (Fibrous) Pleura Tumor (CPT) . . . 666
21.4.7 Primary Squamous Cell Carcinoma of the Pleura . . . 666
21.4.8 Primary Fibrosarcoma . . . 667
21.4.9 Undifferentiated Sarcoma Arising in the Lung and/or Pleura (Formerly Malignant Fibrous Histiocytoma, MFH) . . . 667
21.4.10 Desmoplastic Round Cell Tumor . . . 668
21.5 Metastasis to the Pleura . . . 668
References . . . 671

22 Experimental Lung Tumors . . . 675
22.1 History . . . 675
22.2 Tobacco Inhalation Experiments . . . 675

22.3 Why Adenocarcinomas in Mice and Rats? 675
22.4 Xenograft Transplantation of Human Carcinomas/Cell Cultures into Nude Mice 676
22.5 Differences in Chemically Induced Lung Tumors Compared to Humans 676
22.6 The Urethane Model 676
22.7 Genetically Engineered Mouse Models of Lung Cancer 677
22.7.1 The Pulmonary Adenocarcinoma Models 677
22.7.2 Histopathology of Adenocarcinomas 678
22.7.3 Immunohistochemistry as an Aid to Identify the Precursor Cell Population 682
22.7.4 Progression of Adenocarcinomas 683
22.7.5 Specific Changes Induced by Genetic Modifications 684
22.7.6 Do Mouse Adenocarcinomas Resemble Human Adenocarcinomas? 685
22.7.7 Differences in Mouse and Human Lung Morphology as Explanation for Different Adenocarcinoma Appearance 686
22.7.8 Genetic Differences Between Mouse and Human Adenocarcinomas 686
22.7.9 Cellular Origin of Adenocarcinomas 687
22.7.10 The Small-Cell Carcinoma Models 687
22.8 Models of Metastasis 690
References 691

23 Handling of Tissues and Cells 697
23.1 Biopsies 697
23.2 Videothoracic Lung Biopsy (VATS) and Open Lung Biopsy (OLB) 697
23.3 Resection Specimen 698
23.4 Frozen Section Handling and Evaluation 698
23.5 Handling of Cells 699
23.6 Microbiology 699

Development of the Lung

1

The lung develops from the foregut. At the highness of the later larynx, the single tube splits into two buds for the esophagus and the lower respiratory tract, the "Lungenanlage" [1] (around gestational week 4). Out of this primitive bud, the larynx and the trachea develop, and the trachea finally separates into two bronchial buds. As in general, organogenesis recapitulates also the developmental stages of mammalian lung: a bronchial bud is also formed for a possible mediastinal lobe, as it is found in sheep, swine, and other mammalians. If this bud persists, a median mediastinal bronchial cyst can result [2]. Supernumerary buds are usually deleted by apoptotic mechanisms [3, 4]. Sometimes these buds can give rise to communications with the esophagus [5] or also to bronchogenic cysts [2, 6].

The bronchial buds give rise to several generations of bronchi, starting with the main bronchi, lobar bronchi, segmental bronchi, and so on. In the human lung, approximately 16 generations are formed around the seventh week. After that, bronchioli are formed with an additional of four generations, as membranous, and three generations of terminal respiratory bronchioli. These open into alveolar ducts on which alveoli are grouped.

For the bronchial and alveolar development, the mesenchyme derived from the mesoderm is essential. Each primitive bronchus is surrounded by splanchnopleuromesoderm. Without the connection to the mesoderm, no alveoli develop [7]. Some mediators have been identified, which are responsible for this cooperation between bronchial sprouting and mesenchyme development, such as epimorphin and fibroblast growth factor 7 (FGF7). If this is knocked out, no sprouting does occur [8, 9].

The different developmental stages of the lung are the embryonic stage, where the lung consists of branching tubules (gestational weeks 4–8). These tubules are lined by a single row of high columnar epithelium. In the pseudoglandular phase (weeks 8–16), the branching bronchial tree is embedded in a primitive immature mesenchyme; however, there are so many tubules that it mimics glandular structures (Figs. 1.1 and 1.2).

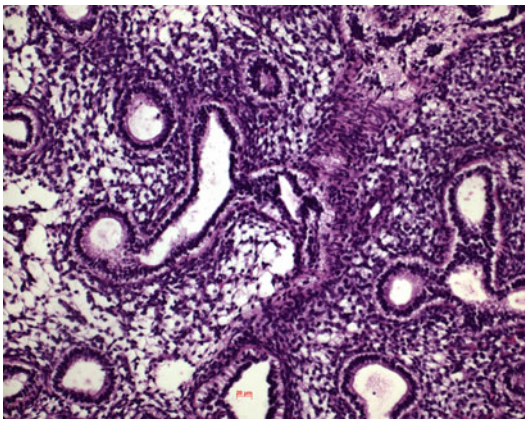

Fig. 1.1 Lung specimen in the early developmental tubular stage, eight week of gestation; the bronchial buds are separated by a primitive mesenchyme, only few primitive endothelial precursor cells can be identified, and capillaries have not been formed. A pulmonary artery has been cut tangentially and is seen between two bronchial buds (*right upper border to middle lower border*). H&E, bar 20 μm

H. Popper, *Pathology of Lung Disease*, DOI 10.1007/978-3-662-50491-8_1

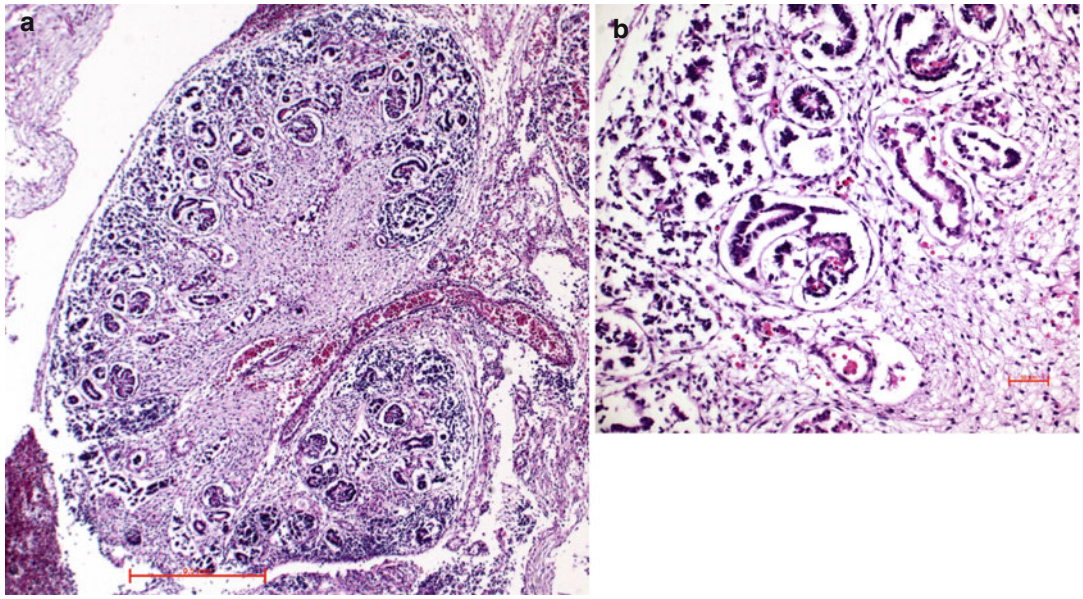

Fig. 1.2 (**a**, **b**) Lung specimen in early developmental glandular stage, 12th gestation week; (**a**) bronchial buds are seen embedded in a primitive mesenchymal stroma, (**b**) but early glands are already formed. H&E, bar 500 and 50 µm

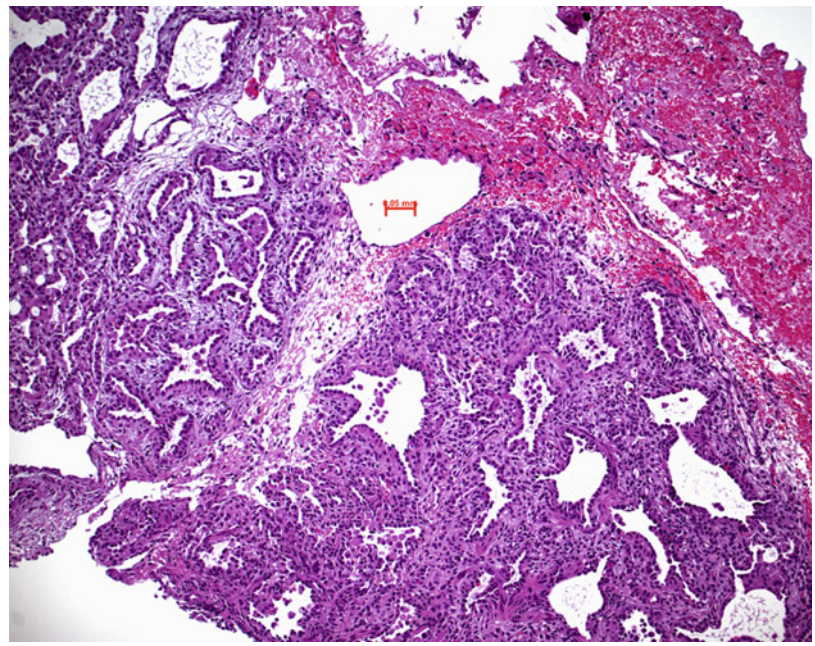

Fig. 1.3 Lung specimen in a premature child (gestation week 24); in transition from canalicular to saccular stage with primitive alveoli, which have not branched, the epithelium already shows pneumocytes in type II, and capillaries are already present; in this case the child developed bronchopulmonary dysplasia. H&E, bar 50 µm

Around the 13th week, the canalicular stage begins lasting until the 25th week. In this stage, the last generations of bronchioli are formed, the epithelium starts to differentiate into pneumocytes type I and II, capillaries are formed around the alveoli, and the bronchi are folded to form the first primitive lobules (Fig. 1.3). The bronchial epithelium also starts from few layers of cells, which expand during development and maturation. Columnar epithelia on H&E-stained section appear as clear cells due to abundant glycogen storage in the cytoplasm, and the nuclei

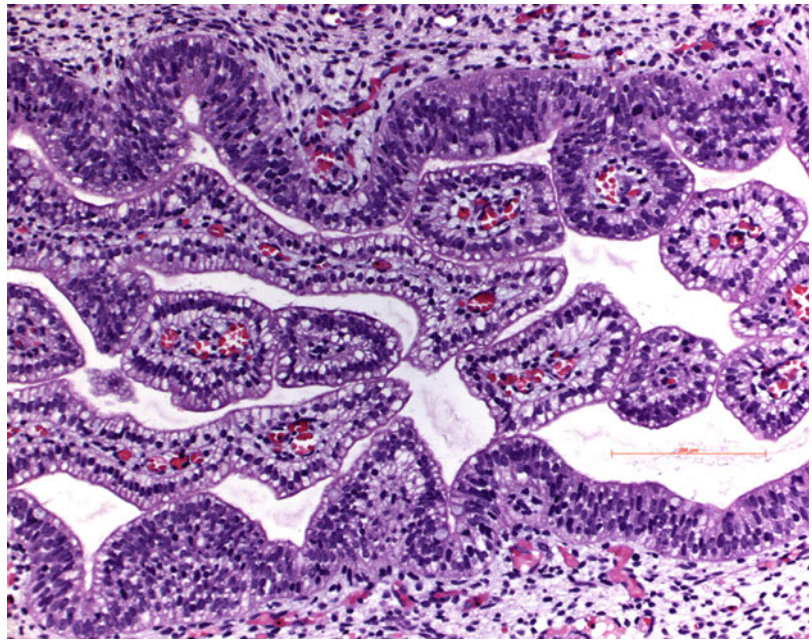

Fig. 1.4 Lung specimen at the development age of 18th gestation week; the bronchial epithelium shows nicely the clear cell pattern with apical positioned nuclei; this changes during maturation: nuclei start to move from the apical to the final basal location within the cell. The clear cell pattern results from abundant glycogen storage, which is dissolved during tissue section processing (alcohol). H&E, bar 200 µm

are positioned at the apical cell portion (Fig. 1.4). During maturation, nuclei move toward the basal portion of the cell, and other structures and proteins replace glycogen granules. In the saccular or terminal sac stage (gestational weeks 24–36), the alveoli are formed, expanded, and capillarized, and surfactant synthesis is started. During the last 2 weeks (alveolar phase), alveoli are expanded, filled by amniotic fluid, secondary septation starts (proceeding still after birth), and respiration starts. In this phase, the fetus already can take up oxygen from the amniotic fluid and release carbon hydroxide. Even after birth bronchial generations and alveoli can be generated [9]. The newborn human has approximately 50 million alveoli at birth, which represents approximately one-sixth of the number of an adult.

The vascular structures arise in two different ways: the large arteries start from the sixth branchial arch and grow along the bronchial tree down to the periphery behind the ductus arteriosus. The veins develop later by sprouting from the left atrium into the mediastinum but in addition also from the sinus venosus. The veins reach the developing primitive lobules and surround them at the surface. Veins primarily form sinusoidal islands and coalesce into conducting structures following the interlobular septa [8, 9]. In contrast the capillaries develop from the mesoderm [10, 11].

Bronchial arteries can be found from the ninth week of gestation. They form a plexus around the bronchi and form anastomoses with the pulmonary veins, whereas a specialized form of blood vessels, the contractile arteries, organizes the connection with the pulmonary arteries. During the saccular stage of the development, the central and peripheral vascular structures are joined. If this program is disturbed, pulmonary sequestration can result, where a part of the peripheral vascular bed is joined to a systemic artery. Also other vascular malformations such as Scimitar syndrome can be based on program failure in this period.

Lymphatic vessels are formed as a plexus in the hilar region together with the ductus thoracicus and are developed at the fifth fetal month.

Nerves are primarily formed out of ganglia of nervus vagus and truncus sympathicus/parasympathicus. An outer and inner plexus is formed around the bronchi, which is finally fused into one plexus at the site of the bronchioles. At the eight month, nerves and ganglia are mature;

neurofilaments can be demonstrated. The nerves can be separated into secretory and sensory as well as motoric fibers. They are close to the bronchial muscles and also around blood vessels.

Neuroendocrine cells (NEC) can be found from the eight gestational weeks on, whereas in bronchioles and alveoli, they can be first demonstrated by neuroendocrine markers around the fifth month (chromogranin A, synaptophysin, PGP9.5). NECs are essential for the proper development and maturation of the bronchial tree.

The other mesenchymal structures, such as myoblasts and chondroblasts, develop from the coelom (splanchnopleura), which surrounds the developing bronchial tree.

The pleura also starts from the coelom (splanchnopleura), which surrounds the "Lungenanlage" [8, 9]. From there the visceral pleura develop. From the pericardo-peritoneal channel, which is the lateral portion of the splanchnopleura, the parietal pleura arises. Primarily the parietal pleura fills both lateral thoracic cavities, since the developing bronchi occupy only small portions of the cavity. The recessus pleura pulmonalis is the only portion, which is free of lung structures.

1.1 Genetic Control of the Development

The organogenesis and maturation of the lung are under the control of genes, which are still only marginally explored. Thyroid transcription factor 1 (TTF1), hepatocyte nuclear factor (HNF3ß), retinoic acid receptor (RAR), Kruppel-like factor 5 (KLF5), and GATA6 all have been identified as differentiation factors for the developing lung [7, 12, 13]. HOX genes and sonic hedgehog (Shh-Gli) are responsible for organogenesis [14]. More specifically FGF2, FGF7, and FGF10 engineer bronchial sprouting [7, 15]. From mouse studies, many more factors are known: The genes listed above act more general, but in the developing bronchial bud, more fine-tuning is required, which is regulated by the interaction of the epithelium and the surrounding mesenchyme. Also NEC play a role: by secreting adrenocorticotropin, in the embryonic and fetal period – rather a growth hormone than an endocrine protein – local growth stimuli are directed toward the dividing bronchial bud, whereas apoptotic mechanisms counteract and abolish supernumerary buds [16–18].

1.2 Comparison of Lung Development Across Species

Within the mammalian family, wide variations are known. In marsupials the young are born with a lung in the pseudoglandular phase; the whole lung development starts after birth. In mice, rats, and hamsters, the young are delivered with lungs in the canalicular phase, and alveoli are formed after birth. In guinea pigs and also in carnivores and sheep, the young have a fully developed lung before birth. Human beings are in between these groups: The alveolar/terminal saccular phase already starts before birth but continues after birth until the fourth to fifth year of postnatal life. After that, the lung still grows in size but the numerical structure is reached [8, 9].

References

1. Miura T. Modeling lung branching morphogenesis. Curr Top Dev Biol. 2008;81:291–310.
2. St-Georges R, Deslauriers J, Duranceau A, Vaillancourt R, Deschamps C, Beauchamp G, Page A, Brisson J. Clinical spectrum of bronchogenic cysts of the mediastinum and lung in the adult. Ann Thorac Surg. 1991;52:6–13.
3. Zylak CJ, Eyler WR, Spizarny DL, Stone CH. Developmental lung anomalies in the adult: radiologic-pathologic correlation. Radiographics. 2002; 22(Spec No):S25–43.
4. Tian J, Mahmood R, Hnasko R, Locker J. Loss of Nkx2.8 deregulates progenitor cells in the large airways and leads to dysplasia. Cancer Res. 2006;66: 10399–407.
5. Srikanth MS, Ford EG, Stanley P, Mahour GH. Communicating bronchopulmonary foregut malformations: classification and embryogenesis. J Pediatr Surg. 1992;27:732–6.
6. Stocker JT. Cystic lung disease in infants and children. Fetal Pediatr Pathol. 2009;28:155–84.
7. Kumar VH, Ryan RM. Growth factors in the fetal and neonatal lung. Front Biosci. 2004;9:464–80.
8. O'Rahilly R, Mueller F. Die Lunge. Edited by Bern, Goettingen, Toronto, Seattle, H. Huber; 1999, p. 275–88.

9. Moore KL, Persaud TVN. Lung development. Elsevier; 2003. p. 267–80.
10. Schachtner SK, Wang Y, Scott Baldwin H. Qualitative and quantitative analysis of embryonic pulmonary vessel formation. Am J Respir Cell Mol Biol. 2000;22: 157–65.
11. de Mello DE, Reid LM. Embryonic and early fetal development of human lung vasculature and its functional implications. Pediatr Dev Pathol. 2000;3:439–49.
12. DeFelice M, Silberschmidt D, DiLauro R, Xu Y, Wert SE, Weaver TE, Bachurski CJ, Clark JC, Whitsett JA. TTF-1 phosphorylation is required for peripheral lung morphogenesis, perinatal survival, and tissue-specific gene expression. J Biol Chem. 2003;278: 35574–83.
13. Wan H, Luo F, Wert SE, Zhang L, Xu Y, Ikegami M, Maeda Y, Bell SM, Whitsett JA. Kruppel-like factor 5 is required for perinatal lung morphogenesis and function. Development. 2008;135:2563–72.
14. Grier DG, Thompson A, Lappin TR, Halliday HL. Quantification of Hox and surfactant protein-B transcription during murine lung development. Neonatology. 2009;96:50–60.
15. Yu S, Poe B, Schwarz M, Elliot SA, Albertine KH, Fenton S, Garg V, Moon AM. Fetal and postnatal lung defects reveal a novel and required role for Fgf8 in lung development. Dev Biol. 2010;347:92–108.
16. Borges M, Linnoila RI, van de Velde HJ, Chen H, Nelkin BD, Mabry M, Baylin SB, Ball DW. An achaete-scute homologue essential for neuroendocrine differentiation in the lung. Nature. 1997;386: 852–5.
17. Cutz E, Yeger H, Pan J. Pulmonary neuroendocrine cell system in pediatric lung disease-recent advances. Pediatr Dev Pathol. 2007;10:419–35.
18. McGovern S, Pan J, Oliver G, Cutz E, Yeger H. The role of hypoxia and neurogenic genes (Mash-1 and Prox-1) in the developmental programming and maturation of pulmonary neuroendocrine cells in fetal mouse lung. Lab Invest. 2010;90:180–95.

Normal Lung

2

In this chapter, we will focus on all aspects of the anatomy and histology of the lung as far as necessary to understand lung function in disease. This chapter does not aim to replace textbooks on anatomy, histology, and lung physiology. More detailed information can be found in these books.

2.1 Gross Morphology

In humans two lungs are formed. In some mammalians, an additional mediastinal lobe is generated, which has its own bronchus directly branching off from the trachea. Both lungs fill the thoracic cavities leaving the midportion for the mediastinal structures and the heart and the posterior midportion for the esophagus and other structures of the posterior mediastinum. The lungs are covered by the visceral pleura, whereas the thoracic wall is internally covered by the parietal pleura. Both merge at the hilum of each lung. The right lung consists of three lobes, the left of two lobes, upper, middle, and lower lobes (Fig. 2.1). The normal lung of an adult weighs 350 (right) to 250 g (left); the lung volume varies individually between 3.5 and 8 L.

Each lobe is further divided into segments (Fig. 2.2). Each upper lobe has three segments, apical, posterior, and anterior, usually numbered accordingly from 1 to 3. In the right lung, the middle lobe is divided into a lateral (4) and a medial (5) segments. On the left side, two further bronchi are found supporting the lingula with a superior (4) and inferior (5) segment. Both lower lobes are divided into a superior (6), mediobasal (7), anterobasal (8), laterobasal (9), and posterobasal (10) segment. The segments are composed of subsegments, which can, however, anatomically not be separated.

Fig. 2.1 Paper mount section of the right lung; the fissure between the upper and lower lobe is seen; the central hilar structures are represented by pulmonary arteries and bronchi

H. Popper, *Pathology of Lung Disease*, DOI 10.1007/978-3-662-50491-8_2

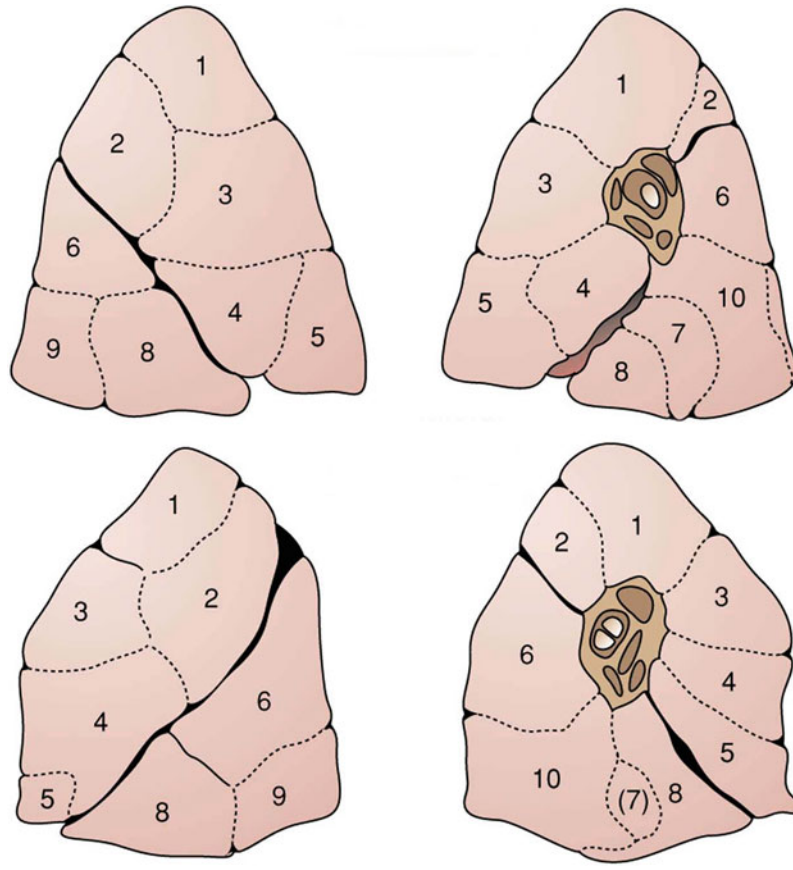

Fig. 2.2 Schematic representation of lung segments, *right upper panel*, *left lower panel*

An alveolar duct together with his alveoli forms the primary lobule. This lobule is difficult to identify on histology (easier in children's lung) and impossible on CT scan. A terminal bronchiole III splits into several alveolar ducts, is larger, and can be identified on CT scan. Histologically this secondary lobule can also be identified by its interlobular septa. Between alveoli pores do exist (pores of Kohn), which permit gas exchange between primary lobules (Fig. 2.3). Between lobules another connecting structure, the channels of Lambert, permits gas exchange.

Fissures are separating the lobes on each site. These are formed by visceral pleura. The fissures between the lower and the middle/lingula and upper lobe are usually well developed and can be followed almost to the hilum. The fissure between the upper and middle lobe clearly separates the

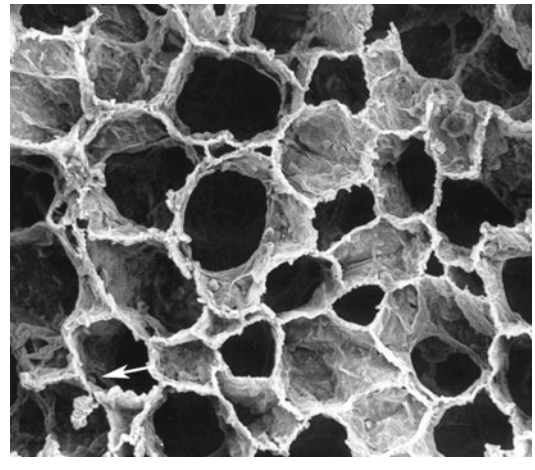

Fig. 2.3 Scanning electron micrograph showing alveolar tissue. The epithelial layer is characterized by *grayish color*, whereas the stroma is more dense and therefore *white*. An *arrow* points to a pore of Kohn