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John P. Lynch *Editors*

Molecular Pathology of Neoplastic Gastrointestinal Diseases

Springer

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Molecular Pathology of Neoplastic Gastrointestinal Diseases

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Preface

Critical molecular mechanisms underlying gastrointestinal (GI) neoplasia have been substantially unraveled in recent years. This has resulted from technological advances such as the genome project data and large-scale "omic" methods, combined with the application of classic molecular and chemical testing approaches and established procedures for pathologic evaluation of tissue and cellular samples. This progress is leading to the development of new approaches for treatments and, in parallel, novel diagnostic workups of gastrointestinal cancers, integrating specific molecular testing in routine pathology practice. Moreover, identification of disease susceptibly genes has enabled the medical community to better manage and prevent diseases that have hereditary traits.

While significant advances have been harnessed, much remains to be learned in the spectrum of neoplastic diseases of the gastrointestinal tract. Critical elements of research that have allowed progress in the various fields of GI neoplastic disease include the availability of animal models, cell culture models, and basic and translational research approaches utilizing prospective or archived specimen material, and such advances are reviewed here.

In this book, we review the molecular aspects that characterize the spectrum of neoplasms that affect the GI tract, providing the reader with up-to-date knowledge at the level of (1) the molecular basis of the individual neoplasms, spanning the carcinomas of esophagus, stomach, small bowel, colon, and rectum; neuroendocrine tumors; and gastrointestinal stromal tumors; (2) molecular testing approaches for diagnosis or for characterization of target genes for selective targeted therapies, with a review of recommended guidelines for clinical application whenever available; (3) molecular testing for hereditary predisposition or disease risk for GI cancers.

The last three chapters in the book are forward-looking, focused on the molecular mechanisms of metastasis, detection of circulating tumor cells and nucleic acids, and the use of tumor markers for gastrointestinal cancers. These are current areas of research interest and future clinical practice and serve to complement the information reviewed for the individual neoplasms.

It is clear that the rapid pace of discovery is unmatched by the definitive validation of many molecular alterations that are identified through ongoing basic and translational research of cancer. Given this scenario we felt it would be impractical to provide coverage of all areas of research in each tumor type, and ultimately, authors for each of the chapters identified what in their opinion are the most relevant topics to cover for each tumor type at the time of writing, realizing that novel findings that may be clinically relevant may become a reality as the book is published. Nevertheless, basic principles of molecular pathogenesis and diagnosis of GI cancers are extensively covered and will remain a foundation for clinical practice as new knowledge emerges.

We expect that this book will be useful to a large spectrum of professionals, from pathologists, laboratorians, clinical gastroenterologists and oncologists, and trainees at various levels such as medical students, residents, fellows, and postdoctoral fellows, as well as investigators interested in the area of gastrointestinal cancer.

New York, NY, USA — Antonia R. Sepulveda, MD, PhD
Philadelphia, PA, USA — John P. Lynch, MD, PhD

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Part I

Introduction

Mechanisms of Gastrointestinal Carcinogenesis

1

Frank I. Scott and John P. Lynch

Introduction

The burden of neoplastic diseases of the gastrointestinal tract is ever growing. Gastrointestinal malignancies are a leading cause of morbidity worldwide. GLOBOCAN Data from 2008 estimate the overall annual incidence of GI malignancies to be 3.8 million cases per year, with a mortality of 3.2 million persons per year.[1,2] Given these extraordinary numbers of affected patients, a tremendous amount of resources have been expended in a quest to understand, prevent, and treat these diseases over the past 40 years. We now know that malignancies of the gastrointestinal tract are heterogeneous in composition, involving a complex interaction between environmental and host factors. This interaction can result in conversion of normal mucosa to precursor lesions, premalignant lesions, and eventual frank malignancy. Despite differences between malignancies in differing cell types and tissues, there are some common themes shared amongst them.

Cells that have undergone neoplastic transformation lose the ability to respond appropriately to signals regulating cell differentiation, replication, migration, and apoptosis. Neoplasms can develop in any organ of the GI tract and from any tissue in the body and can result in extrinsic compression or invasion, consumption of metabolic resources, and metastatic spread to distant sites in the body. Tumors can therefore significantly impact patient health, regardless of whether they are benign or malignant.

This chapter will aim to demonstrate the underlying molecular mechanisms and genetic basis for gastrointestinal malignancies, focusing on the key principles of oncogenesis and molecular steps involved in initiation, evolution, and progression of gastrointestinal malignancy.

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Basic Concepts of Cancer Pathogenesis

Cancer Is a Disease of Gene Mutations

Foremost among the results of the modern molecular revolution is the recognition that many human disease conditions are, fundamentally, caused by mutations in genes. Gastrointestinal cancers are no different. Cancers arise because cells have inherited or acquired mutations in critical genes that regulate cell proliferation, differentiation, and apoptosis. These cells experience disorganized cell division and unregulated growth, which also predisposes the cell to further mutation events. This disordered, unregulated growth leads to the formation of clinically observable tumors. Genetic mutations involved in neoplastic transformation fall into two categories: (1) gain-of-function events, which typically involve oncogene or proto-oncogene activation, and (2) loss-of-function events, typically involving disruption of tumor suppressors.[3] A number of different molecular events can produce gain-of-function (proviral insertion, gene amplification, chromosomal translocations, point mutations, and small deletions) or loss-of-function changes (gene deletions, point mutations, chromosomal rearrangements, and epigenetic gene silencing). One important focus of current research efforts is to utilize novel sequencing and microarray technologies to minutely map and catalogue the many genetic and epigenetic changes that occur in human cancers.

Carcinogenesis Is a Multistep Process

The development of gastrointestinal malignancy usually occurs in a multistep fashion, with malignant neoplastic cells arising from dysplastic tissue (Fig. 1.1). In the colon,

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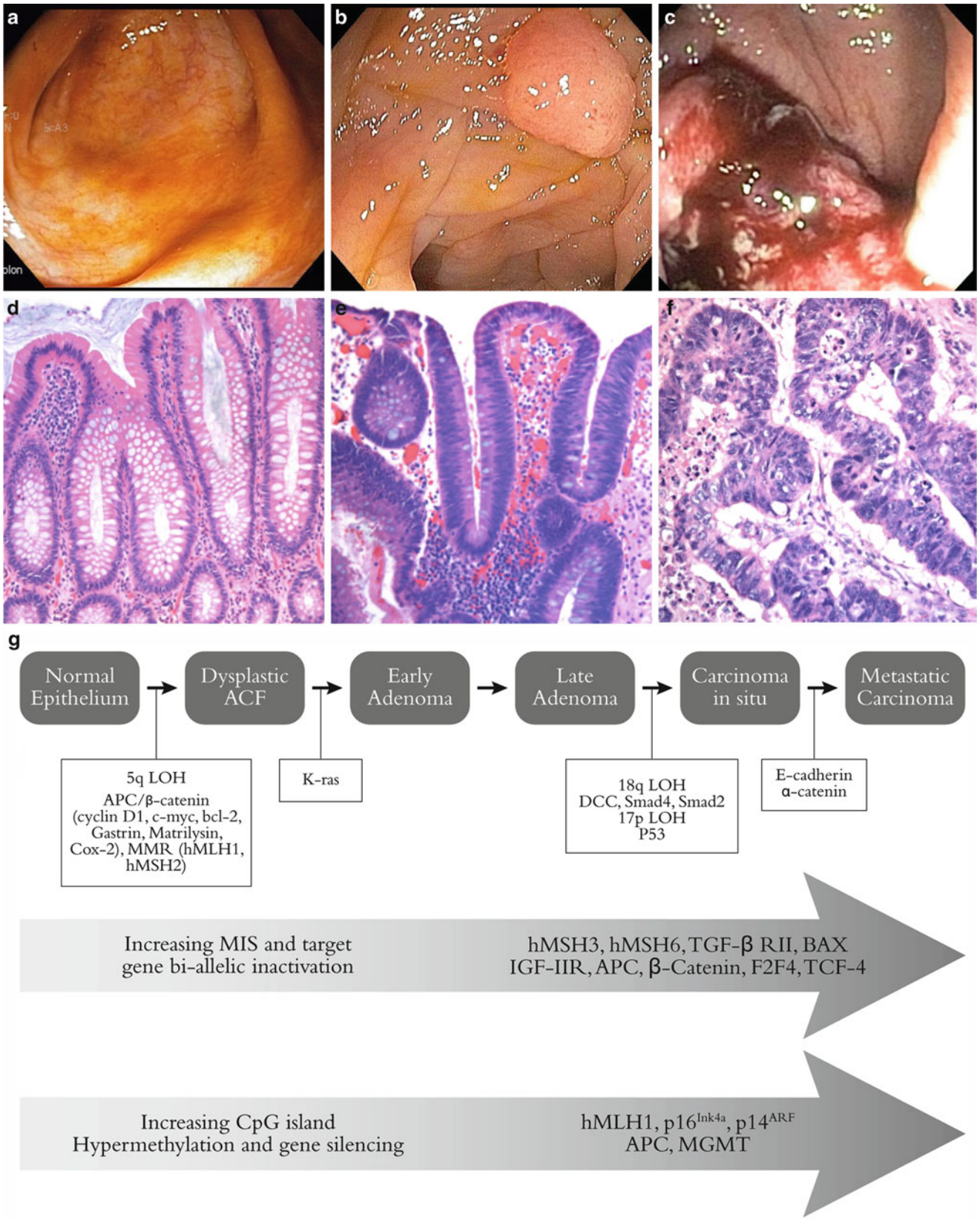

Fig. 1.1 Colon cancer develops in a multistep fashion, progressing from normal mucosa (**a**, **d**) (seen here endoscopically and histologically), with microscopic foci of dysplasia as mutations accumulate. Subsequently, adenomas form (**b**, **e**), with further accumulation of mutations. Neoplastic transformation can then occur with the development of adenocarcinoma (**c**, **f**). An example of the typical progression at the genetic level is also demonstrated (**g**) with examples of mutations that can occur at various points in the progression from normal mucosa to adenoma to carcinoma. *MSI* microsatellite instability. *Pathology images courtesy of Antonia R. Sepulveda, MD, PhD*

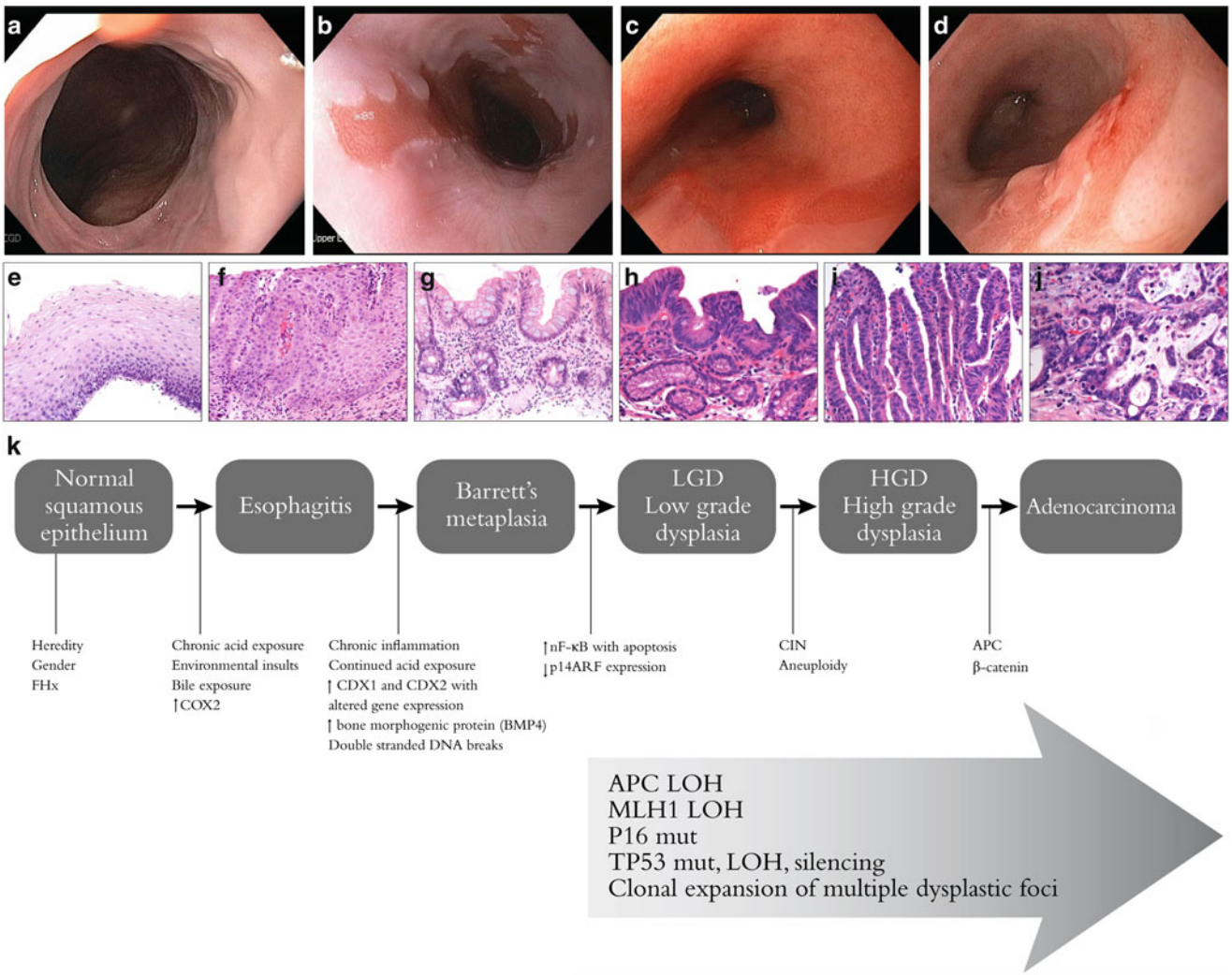

Fig. 1.2 The progression from normal squamous cell mucosa (**a**, **e**) to esophagitis (**f**) to Barrett's esophagus (**b**, **g**), followed by low-grade dysplasia (LGD) (**h**), high-grade dysplasia (HGD) (**c**, **i**), and finally to esophageal adenocarcinoma (**d**, **j**), as seen here endoscopically and histologically, is not as uniform at a genetic level as in colon cancer. Despite this, the process is similar (**k**), with genetic predispositions and environmental insults resulting in chronic inflammation. This inflammation results in Barrett's metaplasia, with subsequent altered gene expression and subsequent development of various mutations and eventual neoplastic transformation. *Endoscopic images courtesy of Dr. Gary W. Falk, M.D., M.Sc. Pathology images courtesy of Antonia R. Sepulveda MD, PhD*

this progression from normal mucosa to dysplastic foci to eventual invasive carcinoma is represented by the adenoma–carcinoma sequence, and has been demonstrated in pathologic, epidemiologic, and animal studies.[4–7] The earliest histologically definable lesions in this sequence are aberrant crypt foci (ACF). ACF are crypts that appear larger and thicker than normal, with increased luminal diameter and an opening that can be slit-like or serrated. They were first identified by methylene blue stain in azoxymethane-treated mice.[8–10] It is estimated that 65–95% of human ACF are hyperplastic, but a significant proportion are dysplastic and are considered to be similar to adenomatous polyps.[11–13] Genetic analysis of these lesions has demonstrated that they share many of the same mutations present in adenomas.[8,13–20]

Similar progressions from normal mucosa to dysplasia to malignancy have been described for esophageal cancer, gastric cancer, and pancreatic cancer. In esophageal adenocarcinoma, malignancy is preceded by a premalignant metaplasia known as Barrett's esophagus. Barrett's is an intestinal-type metaplasia that arises in the setting of chronic gastroesophageal reflux disease.[21] Barrett's metaplasia is not dysplastic, but can progress to dysplasia and adenocarcinoma in a significant number of patients (Fig. 1.2). Similar patterns of progression from established precursor lesions to dysplasia to neoplasia have been documented in the stomach (gastritis > atrophy > intestinal metaplasia > dysplasia > cancer) and in pancreatic cancer (PanIN1a > PanIN1b > PanIN2 > PanIN3) as well.[22,23]