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Preface: Molecular Pathology in the Modern Era: Revisiting Jacob's Spotted Sheep xi

Martin H. Bluth

Introduction: The Impact of Molecular Pathology on the Practice of Pathology 749

Martin H. Bluth

Molecular pathology is affecting and influencing the entire clinical laboratory. Furthermore, the union of pathology and molecular medicine continues to mature into an amalgam that will both define and serve the emerging field of personalized medicine. Advances in the understanding of pathobiology, high throughput automation, cost containment, and refined methodology will avail greater diagnostic and prognostic prowess and provide more efficient and appropriate therapeutic selection as well guide effective patient monitoring with respect to disease responses.

Molecular Pathology Techniques 753

Mark J. Bluth and Martin H. Bluth

Molecular pathology techniques have matured considerably over the last decade. New technologies have provided increased sensitivity for improved diagnostic capacity. Furthermore, novel methodologies have matured to interrogate nucleic acid and protein signatures effectively to aid in elucidating the pathophysiology of disease in addition to diagnosis, prognosis, and therapeutic monitoring for patient management. Here general molecular techniques used in the molecular pathology laboratory as they are used for clinical applications are described.

Clinical Implication of MicroRNAs in Molecular Pathology 773

Seema Sethi, Shadan Ali, Dejuan Kong, Philip A. Philip, and Fazlul H. Sarkar

MicroRNAs are small endogenous noncoding RNAs that are critical regulators of several physiologic and pathologic processes including cancers. Variations in the level of microRNA expression have been linked with the development, progression, and spread of cancer to distant organs. These tiny molecules may play a role in accurate and early diagnosis, and also as prognostic determinants. Modulating their activity provides opportunities for developing and designing novel cancer therapeutics. Recent studies indicate their detection in a wide variety of human biologic specimens including blood, serum, fine-needle aspirates, and tissues, making them clinically useful biomarkers of disease for early detection, prognosis, and for designing personalized therapies.

Diagnostic Molecular Microbiology: A 2013 Snapshot 787

Marilynn Ransom Fairfax and Hossein Salimnia

Molecular testing has a large and increasing role in the diagnosis of infectious diseases. It has evolved significantly since the first probe tests were

FDA approved in the early 1990s. This article highlights the uses of molecular techniques in diagnostic microbiology, including "older," as well as innovative, probe techniques, qualitative and quantitative RT-PCR, highly multiplexed PCR panels, some of which use sealed microfluidic test cartridges, MALDI TOF, and nuclear magnetic resonance. Tests are grouped together by technique and target. Tests with similar roles for similar analytes are compared with respect to benefits, drawbacks, and possible problems.

Molecular Pathology in Transfusion Medicine **805**

Matthew B. Elkins, Robertson D. Davenport, Barbara A. O'Malley, and Martin H. Bluth

This article provides an overview of the application of molecular diagnostic methods to red cell and platelet compatibility testing. The advantages and limitations of molecular methods are evaluated compared with traditional serologic methods. The molecular bases of clinically significant red cell and platelet antigens are presented. Current recommendations for reporting molecular assay results and distinctions between genotype and phenotype are discussed.

Molecular Diagnosis of Hematopoietic Neoplasms **817**

Radhakrishnan Ramchandren, Tarek Jazaerly, and Ali M. Gabali

Cytogenetic abnormalities are considered to be common events in hematologic malignancies. These abnormalities generally consist of structural chromosomal abnormalities or gene mutations, which often are integral to the pathogenesis and subsequent evolution of an individual malignancy. Improvements made in identifying and interpreting these molecular alterations have resulted in advances in the diagnosis, prognosis, monitoring, and therapy for cancer. As a consequence of the increasingly important role of molecular testing in hematologic malignancy management, this article presents an update on the importance and use of molecular tests, detailing the advantages and disadvantages of each test when applicable.

Molecular Diagnostics in Colorectal Carcinoma **835**

Amarpreet Bhalla, Muhammad Zulfiqar, Michael Weindel, and Vinod B. Shidham

Molecular pathogenesis and classification of colorectal carcinoma are based on the adenoma-carcinoma sequence in the Vogelstein model, serrated polyp pathway, and microsatellite instability. The genetic basis for hereditary nonpolyposis colorectal cancer is based on detection of genetic mutations. Genetic testing for Lynch syndrome includes microsatellite instability, methylator phenotyping, BRAF mutation, and molecular testing. Molecular makers include quantitative multigene reverse transcriptase–polymerase chain reaction assay and KRAS and BRAF mutation analysis. Potential biomarkers include one-step nucleic acid amplification and epigenetic inactivation of endothelin 2 and endothelin 3 in colon cancer. Molecular screening approaches in colorectal cancer using stool DNA are under investigation.

Molecular Diagnostics in the Neoplasms of Small Intestine and Appendix 861

Amarpreet Bhalla, Muhammad Zulfiqar, Michael Weindel, and Vinod B. Shidham

Adenocarcinoma of the small intestine is relatively rare in comparison to colorectal carcinoma. Adenocarcinoma of the small intestine arises through the adenoma-carcinoma sequence in the colon. However, adenocarcinomas arising in the background of inflammatory bowel disease develop through the dysplasia-carcinoma sequence. Most of the cases occur in the duodenum; however, adenocarcinoma occurring in association with Crohn disease is more common in the ileum.

Molecular Diagnostics in Esophageal and Gastric Neoplasms 867

Muhammad Zulfiqar, Amarpreet Bhalla, Michael Weindel, and Vinod B. Shidham

Esophageal carcinoma is the most rapidly increasing tumor in incidence in the United States. It has an established association with a precursor lesion (Barrett esophagus). Gastric carcinoma (GC) is the second leading cause of cancer death in the world. The prognosis for patients with advanced stage GC and esophageal carcinoma is poor. Human epidermal growth factor 2 (HER-2) overexpression is seen in gastroesophageal junction carcinoma and a subset of GC. HER-2 overexpressing tumors are eligible for HER-2 targeted therapies, which lead to a better survival in these patients.

Molecular Diagnostics in the Neoplasms of the Pancreas, Liver, Gall Bladder, and Extrahepatic Biliary Tract 875

Michael Weindel, Muhammad Zulfiqar, Amarpreet Bhalla, and Vinod B. Shidham

Pancreatic neoplasms, including ductal adenocarcinoma, intraductal papillary mucinous neoplasm, solid pseudopapillary neoplasm, pancreatic endocrine neoplasms, acinar cell carcinoma, and ampullary carcinoma, are associated with different genetic abnormalities. Liver neoplasms, including hepatic adenomas, hepatocellular carcinomas, and cholangiocarcinomas, are associated with identifiable risk factors and genetic changes. Gall bladder adenomas and adenocarcinomas arise from distinct molecular pathways. The molecular abnormalities seen in these tumors are not used routinely in the molecular diagnostic laboratory.

Current Applications of Molecular Genetic Technologies to the Diagnosis and Treatment of Cutaneous Melanocytic Neoplasms 881

Muhammad Zulfiqar and Andrew David Thompson

Decades of research have brought knowledge to a point where physicians are beginning to understand human disease processes like oncogenesis on a molecular level. Molecular technologies are now being applied to current clinical settings such as the diagnosis and treatment of cutaneous melanocytic neoplasms. In particular, dermatopathologists are using fluorescence in situ hybridization to aid in the diagnosis of challenging melanocytic neoplasms. Pathologists are working with oncologists to use the sequences of specific genes in melanomas to choose more effective

treatments. This article discusses how these technologies are altering the ways in which cutaneous melanocytic neoplasms are diagnosed and treated.

Breast Carcinoma: Molecular Profiling and Updates **891**

Sudeshna Bandyopadhyay and Rouba Ali-Fehmi

The most significant contribution of molecular subtyping of breast carcinomas has been the identification of estrogen-positive and estrogen-negative tumor subtypes, which are 2 distinct entities with differing prognoses and requiring different therapy. Molecular and genetic analyses can provide prognostic information; however, a thorough histopathologic evaluation with an evaluation of predictive biomarkers will provide similar information. Knowledge of genetic alterations in these tumors will help identify novel therapeutic targets, which might have an impact on prognosis. Understanding the progression pathways involved in the transition of in situ carcinoma to invasive carcinoma might lead to efficient risk stratification in these patients.

Gynecologic Cancers: Molecular Updates **911**

Quratulain Ahmed, Baraa Alosh, Sudeshna Bandyopadhyay, and Rouba Ali-Fehmi

This article reviews the molecular features and pathogenesis of gynecologic malignancies. Understanding the molecular basis of endometrial carcinoma helps to provide an explanation for the prognosis of these tumors and opens up avenues for research into novel therapies that may prove beneficial.

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