Focusing on Preinvasive Neoplasia
A Molecular Frontier at the Pathologist’s Fingertips

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The last decade has brought forth an unprecedented expansion of knowledge regarding the molecular biology of neoplasia. The critical role of oncogene addiction in tumorigenesis, bolstered by the identification of oncogenic activation in a wide variety of rare and common cancers, has resulted in a fruitful partnership of molecular pathology in the characterization of cancer with pharmaceutical research focused on development of targeted therapies. These targeted therapies seek to break the cycle of oncogenic activation, using the cancer cell’s dependency on these growth signals as a vulnerability. Within this decade, we have seen advances in the treatment of a multitude of tumor types. These partnerships of oncology, pathology, basic science, and pharmaceutical industry continue to reap benefits for patients with advanced malignancy who are seeking novel effective therapies.

The successes are monumental. However, in reviewing current guidelines for molecular testing in a variety of tumors, for example, as part of the National Comprehensive Cancer Network, these state-of-the-art advances are generally for advanced-stage cancer patients. This is especially true in solid tumors. In addition, beyond these guidelines, approaches in cancer care that incorporate high-throughput molecular characterization are largely focused on the discovery of a tumor-specific alteration that may lead to the identification of an individual vulnerability for a particular patient’s cancer. Again, although very important, these cutting-edge efforts continue to reap benefits for patients with advanced-stage disease who have failed conventional therapy.

As we reflect back on approaches that may reduce cancer mortality on a population scale—that is, reduce cancer overall—molecular pathology itself has had a smaller impact. We consider a relatively simple test such as the Papanicolaou (Pap) smear as having had a major influence on the reduction of death from cervical cancer in the United States. Although this test has been improved over the years and has been enhanced by molecular testing for human papillomavirus (HPV), the underpinning of success lies in the understanding of the stepwise progression of neoplasia from its earliest morphologic manifestation with an intervention at its earliest stages. We look at the reduction in lung cancer incidence and see the impact of smoking cessation programs, and we hope that early detection through computed tomography screening programs will build on the successes of smoking cessation in patients already exposed to the carcinogenic effects of cigarette smoking. We can support the efforts to further reduce death from breast cancer and colon cancer through already successful early detection programs.

The understanding of the preinvasive neoplasia in these diseases has led to approaches for early detection. It underscores the notion that the more we understand about these early steps, the more we can do to develop tests to identify and potentially intervene in these early lesions, either eradicating them or delaying invasive progression. In doing so, different partnerships than those that have been so effective in developing approaches to advanced disease will need to be created. This may include novel approaches to imaging, molecular testing, and biomarker testing, and will require expanded relationships of basic science, translational molecular pathology, radiology, medicine, and segments of industry focused on such biomarker development.

With this in mind, the group at Weill Cornell Pathology and invited colleagues were charged with the task of reviewing our current understanding of precursor lesions in a variety of cancer types. In their work, Drs Pittman, Rao, and Hruban evaluate the current knowledge of preinvasive pancreatic neoplasia and its relationship to invasive pancreatic adenocarcinoma. Pancreatic carcinoma is a highly aggressive neoplasm with a high mortality, and early detection would have critical impact in this disease. Their review highlights an approach that has combined detailed analysis of stepwise molecular changes with imaging and cytologic approaches to identify a subset of patients for whom an intervention can be proposed. As the authors point out, there is vast molecular knowledge in this area, but the ability to intervene remains a critical future frontier.

Drs Khani and Robinson review what is known about precursors of prostate cancer, bladder cancer, renal carcinoma, and testicular cancer from a morphologic and molecular point of view. In their analysis, the morphologic detection of these lesions is not always possible and molecular detection is still a growing field, so that the interception of preinvasive disease remains a major challenge in this area.

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Dr Pisapia examines the current correlates of an increasingly molecular classification of gliomas. What is striking about this group of tumors is that the cell of origin or preinvasive lesion in brain tumors remains largely unknown from an imaging or morphologic perspective, and as such, discussions of causative factors and early interventions remain extremely speculative.

The review of precursor lesions of the thyroid by Dr Scognamiglio highlights current thinking regarding the relationship of molecular alterations and neoplasia of the thyroid. Thyroid cancer presents a different twist on the issue of precursor identification—that the dividing line among early lesions has impact on the definition of carcinoma, and as a result impacts therapy, in this case preventing overtreatment.

Dr Pirog’s review examines HPV-associated glandular lesions of the cervix, as well as HPV-negative lesions. The success of screening Pap stains in cervical squamous lesions unearthed the need for detection of lesions that are difficult to identify by Pap test. Atypical glandular cells detected morphologically, although challenging, can be combined with HPV testing to capture a significant proportion of these adenocarcinomas. As a result, a rarer but diagnostically vexing group of HPV-negative cervical adenocarcinomas has come to light that may need a different morphologic, immunohistochemical, and molecular approach.

In their examination of lobular carcinoma in situ of the breast, Drs Ginter and D’Alfonso look at the history and evolution of our understanding of this lesion, putting it into the context of known and emerging molecular pathogenesis. What to do upon detection of lobular carcinoma in situ—that is, careful follow-up, chemoprevention, or surgery—depends upon an integration of epidemiologic, imaging, and histologic findings that may in the future be impacted by molecular testing for the detection of favorable or adverse markers.

This state-of-the-art collection of reviews provides insight into the progress needed in this field. As the feasibility of high-throughput genomic approaches increases in small paraffin-embedded samples, cytology, and peripheral blood, the potential for pathologists to redefine these precursor lesions in a clinically relevant context also increases. Pathologists must lead the exploration into this frontier, and we are uniquely positioned to unlock its mysteries.

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