Cancer Biomarkers 4 (2008) 285–286
IOS Press

Editorial

Targeted Imaging of Neoplasia in the Digestive Tract

Thomas D. Wang*
Division of Gastroenterology and Hepatology, University of Michigan School of Medicine, 109 Zina Pitcher Place, BSRB 1522, Ann Arbor, MI 48109, USA

In this issue of *Cancer Biomarkers*, we discuss the emergence of novel molecular probes and endoscopic instruments for performing targeted imaging of neoplasia in the digestive tract. The digestive tract is an ideal place to develop these emerging methods, in particular for clinical applications because these hollow organs are easy to access with endoscopy and exogenous probes can be topically applied safely. The role of imaging is becoming ever more important as a clinical tool for assessing cancer biomarkers. Spatial information provides a powerful resource to guide tissue biopsy, stratify risk patients, monitor therapeutic response, and assess tumor recurrence. Moreover, we have recently experienced greater understanding of the sequence of genetic and molecular changes that lead to clonal selection and growth advantages for cancerous cells in the digestive tract [1–3]. This research has revealed the timing of expression of key molecular targets so that we can perform earlier detection of diagnostic cancer biomarkers with imaging methods. We are now beginning to see a convergence in our knowledge of molecular biology, development of affinity probes, and performance of imaging instruments. These factors are interdependent and must develop together as we head in the direction of personalized medicine [4]. Currently, physicians make clinical decisions to diagnose and stage cancer based primarily on structural abnormalities, including mass effect, texture variations, and interval change. While this strategy has been successful for some clinical applications, this approach can be greatly improved by incorporating the molecular features of tissue that reveal mucosal function. Use of this information is important because changes in molecular expression occur well before that of structural features. Moreover, most forms of cancer in the digestive tract develop slowly over many years, and dwell in a premalignant phase that offers a window of opportunity for early detection. Thus, if effective methods of imaging to target early cancer biomarkers can be adequately developed, we may see a new paradigm emerge for prevention, screening, and management of cancer in the digestive tract.

Targeted imaging requires the detection of molecular changes in cells associated with disease. Molecular targets are usually too small to be visualized directly, thus probes that are fluorescence or radio labeled are needed to reveal biomarker expression with high contrast. The first paper by Elias et al. discusses activatable molecular probes, which have generated tremendous promise for distinguishing between neoplastic and normal mucosa in the digestive tract. These reagents are designed to elicit a detectable change in fluorescence signal upon interacting *in vivo* with a biomarker of cancer. The best developed probes in this class are activated within cells through enzymatic reactions, and can produce very high target-to-background ratios. New designs of activatable probes, their applications for optical and MRI imaging, and practical use for visu-

*Thomas D. Wang, MD, PhD. Tel.: +1 734 936 1228; Fax: +1 734 647 7950; E-mail: thomaswa@umich.edu.

ISSN 1574-0153/08/$17.00 © 2008 – IOS Press and the authors. All rights reserved

alizing cancer biomarkers *in vivo* are discussed in this issue. Furthermore, the emergence of nanotechnology provides an entirely new set of tools for imaging molecular expression *in vivo*. In particular, semiconductor quantum dots have demonstrated superior optical properties for imaging cancer biomarkers in comparison to that of conventional organic dyes. Quantum dots offer significant enhancements in performance that include a broad spectral range, tunable fluorescence emission, improved signal intensity, long term photostability, and biological functionality. In this issue, Xing et al. explain the principles of quantum dots, including the fundamental physics, optical properties, biofunctionization strategies, and *in vivo* imaging applications. Next, Muguruma et al. present methods for performing targeted imaging of neoplasia in the digestive tract using near-infrared fluorescence endoscopy to detect anti-CEA and anti-MUC1 antibodies labeled with indocyanine green derivatives for detection of gastric cancer. A near-infrared instrument represents an important technological advance because greater tissue penetration and less tissue autofluorescence can be achieved in this spectral regime than with visible light. Fluorescence-labeled antibodies are high affinity probes that have been developed to detect over expressed cell surface targets found in neoplastic mucosa. CEA functions in cell adhesion, and MUC1 binds to pathogens and performs cell signaling [5,6]. These targets are both membrane-associated glycoproteins that are commonly found in glandular epithelium of the digestive tract.

Advances have also been made in the development of novel methods for targeted imaging based on endoscopy to perform early detection of colorectal and esophageal cancer, discussed in the papers by Hsiung et al. and Lu et al., respectively. The aim of these techniques is to reveal functional information about the mucosa based on patterns of molecular expression. These images are combined with architectural features provided by conventional white light endoscopy. In addition, a greater understanding of the significance and timing of over expressed molecular targets has been achieved using comprehensive methods of biological evaluation such as gene expression profiling and high throughput analyses. These studies have identified a number of promising intracellular and cell surface targets expressed by the mucosa of the digestive tract that can reveal evidence for neoplastic transformation. In addition, the development of peptides as affinity probes that produce high target-to-background ratio, offer binding specificity, and have safe toxicity profiles is presented. Specifically, peptides have shown promise for use as molecular probes in the digestive tract because of their high diversity, rapid binding kinetics, low immunogenicity, ease of labeling, and low production costs. Moreover, improved imaging instruments that are sensitive to fluorescence, including wide area endoscopy and confocal microscopy, are maturing and promise to improve performance for visualizing probe binding. These exciting new techniques have great potential to improve the detection sensitivity, increase surveillance efficiency, and ultimately achieve better patient outcomes for management of cancer in the digestive tract. As progress in these areas continues, physicians will soon have powerful new tools for diagnosing and treating patients with digestive diseases.

References

[1] C.C. Maley, P.C. Galipeau, J.C. Finley et al., Genetic clonal diversity predicts progression to esophageal adenocarcinoma, *Nat Genet* **38**(4) (2006), 468–473.

[2] J.H. Lee, S.J. Park, S.C. Abraham et al., Frequent CpG island methylation in precursor lesions and early gastric adenocarcinomas, *Oncogene* **23**(26) (2004), 4646–4654.

[3] C.P. Giacomini, S.Y. Leung, X. Chen et al., A gene expression signature of genetic instability in colon cancer, *Cancer Res* **65**(20) (2005), 9200–9205.

[4] W.C. Eckelman, R.C. Reba and G.J. Kelloff, Targeted imaging: an important biomarker for understanding disease progression in the era of personalized medicine, *Drug Discov Today* **13**(17–18) (2008), 748–759.

[5] P. Kuusela, H. Jalanko, P. Roberts et al., Comparison of CA 19-9 and carcinoembryonic antigen (CEA) levels in the serum of patients with colorectal diseases, *Br J Cancer* **49**(2) (1984), 135–139.

[6] M. Sagara, S. Yonezawa, K. Nagata et al., Expression of mucin 1 (MUC1) in esophageal squamous-cell carcinoma: its relationship with prognosis, *Int J Cancer* **84**(3) (1999), 251–257.