Editorial

Colorectal cancer screening using protected microRNAs

Nathan R. Wall

Center for Health Disparities & Molecular Medicine, Department of Biochemistry & Microbiology, Loma Linda University, Loma Linda, California, USA

J Gastrointest Oncol 2011; 2: 206-207. DOI: 10.3978/j.issn.2078-6891.2011.040

Colorectal cancer is one of the most frequent malignant tumors (1) with the fourth highest incidence and second highest mortality of any cancer in the United States (2). As a result of aggressive screening and education, the last 30 years has shown a significant decrease in US mortality rates. However, in countries where the screening and education have not been as aggressive, and in US patients whose age is below the recommended screening age, the rates are increasing (3). It is therefore important to aggressively investigate all novel, basic science avenues and/or discoveries in the context of colorectal cancer with the ultimate goal of its eradication.

Screening for colorectal cancer involves guaiac-based, fecal occult blood and fecal immunochemical occult blood testing. More recently, the approach to assay stool and bodily fluids from colorectal cancer patients for biomarkers representative of the disease such as APC, p53 and K-Ras have been exploited with limited success. Fecal DNA-based testing, performed on cells sloughed or shed from tumors into the stool has revealed aberrant hypermethylation of CpG islands (4). Though many of these assays have been exploited in the detection of colorectal cancer for the last three decades they are limited due to low specificity and sensitivity. It is therefore important that assays be developed that provide diagnostic information and help in the therapeutic decision for patients suffering with colorectal cancer.

Extracellular membrane vesicles ranging in diameter of 30-150 nm and originating from various cellular origins have been increasingly recognized for their participation in a variety of both normal and pathological cellular processes (5). Regardless of their cell type of origin these membrane bound vesicles or exosomes provide a protected and controlled internal microenvironment outside the cell for metabolic objectives of the host cell to be carried out at a distance from the host cell (6). As was demonstrated by Koga *et al*., (7) in this issue of *Journal of Gastrointestinal Oncology*, these exosomes provide a protective membrane that in the harsh fecal environment increases the stability of their contents. Exosomes are also believed to be instrumental in cell-cell and cell-extracellular communication (8). Moreover, while knowledge of exosome biogenesis and physiological relevance remains limited, accumulating evidence suggests that their bioactivity may be clinically applicable in cancer therapeutics (9).

The content of the exosome and the subsequent biological function depends on the cell of origin. Recent studies have shown that besides protein, RNA and miRNAs are also actively secreted in exosomes that protect them from degradation by RNases (10,11). These proteins and RNAs provide a profile and possible understanding of the cellular proteome and transcriptome at the time of collection. In addition, serial samples identified over time will allow for a robust, simple and noninvasive molecular means to study the evolving genetic changes relative to tumor progression (11) as well as provide a marker of prognosis and therapeutic response using serum, plasma, urine or as is the case of Koga *et al*., feces.

miRNA are small noncoding transcripts that have been identified as cellular molecules with important diagnostic, prognostic and therapeutic implications (12,13). Though their biology is still not entirely understood, each miRNA may control hundreds of mRNA targets, the results of which are to regulate gene expression. Specifically, miRNAs have been shown to reduce the stability of mRNAs involved in inflammation, cell cycle regulation, stress responses, differentiation, apoptosis and invasion (14). Additionally, miRNAs having both tumor-suppression and oncogenic

No potential conflict of interest.

Corresponding to: Nathan R. Wall, Ph.D. M.B.A., M.S. Center for Health Disparities Research & Molecular Medicine, Loma Linda University, 11085 Campus Street, Mortensen Hall, Room 162, Loma Linda, CA 92350. Tel: 909-558-4000 x81397; Fax: 909-558-0177. Email: nwall@llu.edu.

Submitted Sep 01, 2011. Accepted for publication Sep 03, 2011.
Available at www.thejgo.org

ISSN: 2078-6891

functions have been shown to be dysregulated in many types of cancer (15).

Exosomes isolated from feces using immunomagnetic beads proved to have stable miRNA which remained so even when exogenous RNase was added for an additional ninety minutes. Specifically, the colorectal cancer important miRNA, miR-21, which has an enhanced expression in colorectal cancer compared to normal colorectal mucosa, has been shown to be unstable when investigated directly from stool samples. However, when investigation of stool-purified exosomes, miR-21 was protected from the harsh conditions of the feces (7).

Research on tumor-exosomes and their roles as messengers within the tumor microenvironment is an exciting field that continues to stimulate and enhance the field of cancer biology with new ideas, questions and hypotheses. Investigating these hypotheses requires tools to affect the exosome biology including their content and secretion. The study by Koga *et al.*, has important implications for colorectal cancer screening. Koga *et al.* (7), demonstrate that exosomes prevent the RNase-dependent degradation of miRNAs. Indeed, fecal miRNA-based testing, performed on tumor-exosomes sloughed or shed into the stool, will allow molecular-based diagnosis that in time may also aid in therapy decisions and disease response surveillance leading to better management of colorectal cancer.

References

1. Stein U, Schlag PM. Clinical, biological, and molecular aspects of metastasis in colorectal cancer. Recent Results Cancer Res 2007;176:61-80.
2. Davis DM, Marcet JE, Frattini JC, Prather AD, Mateka JJ, Nfonsam VN. Is it time to lower the recommended screening age for colorectal cancer? J Am Coll Surg 2011;213:352-61.
3. Center MM, Jemal A, Ward E. International trends in colorectal cancer incidence rates. Cancer Epidemiol Biomarkers Prev 2009;18:1688-94.
4. Link A, Balaguer F, Shen Y, Nagasaka T, Lozano JJ, Boland CR, et al. Fecal MicroRNAs as novel biomarkers for colon cancer screening. Cancer Epidemiol Biomarkers Prev 2010;19:1766-74.
5. Iero M, Valenti R, Huber V, Filipazzi P, Parmiani G, Fais S, et al. Tumour-released exosomes and their implications in cancer immunity. Cell Death Differ 200815:80-8.
6. Keller S, Sanderson MP, Stoeck A, Altevogt P. Exosomes: from biogenesis and secretion to biological function. Immunol Lett 2006;107:102-8.
7. Koga Y, Yasunaga M, Moriya Y, Akasu T, Fujita S, Yamamoto S, et al. Exosome can prevent RNase from degrading microRNA in feces. J Gastrointest Oncol, 2011;2: 215-22.
8. Al-Nedawi K, Meehan B, Rak J. Microvesicles: messengers and mediators of tumor progression. Cell Cycle 2009;8:2014-8.
9. Couzin J. Cell biology: The ins and outs of exosomes. Science 2005;308:1862-3.
10. Pegtel DM, Cosmopoulos K, Thorley-Lawson DA, van Eijndhoven MA, Hopmans ES, Lindenberg JL, et al. Functional delivery of viral miRNAs via exosomes. Proc Natl Acad Sci U S A 2010;107:6328-33.
11. Skog J, Würdinger T, van Rijn S, Meijer DH, Gainche L, Sena-Esteves M, et al. Glioblastoma microvesicles transport RNA and proteins that promote tumour growth and provide diagnostic biomarkers. Nat Cell Biol 2008;10:1470-6.
12. Ambros V. The functions of animal microRNAs. Nature 2004;431:350-5.
13. Lu J, Getz G, Miska EA, Alvarez-Saavedra E, Lamb J, Peck D, et al. MicroRNA expression profiles classify human cancers. Nature 2005;435:834-8.
14. Farazi TA, Spitzer JI, Morozov P, Tuschl T. miRNAs in human cancer. J Pathol 2011;223:102-15.
15. Munker R, Calin GA. MicroRNA profiling in cancer. Clin Sci (Lond) 2011;121:141-58.