TSPAN8 and LGALS4 combination as blood biomarkers for colorectal cancer detection

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Received: June 03, 2016
Published online: July 11, 2016

Colorectal cancer (CRC) is the third most common cancer in the world and it is a determinant cause of mortality. A significant survival rate is achieved if the disease is detected at an early stage, thus screening represents an important cancer-control tool. Recently we unveiled a panel of mRNAs, which if isolated in whole blood represent an efficient screening test for colorectal cancer. These mRNA molecules as a biomarker in blood by qRT-PCR assay offer a test with high sensitivity and specificity for clinical diagnostics. The expression of 4 genes: TSPAN8, LGALS4, COL1A2 and CEACAM6 proved to be statistically different between patients and healthy controls. The diagnostic accuracy, in terms of specificity and sensitivity of the TSPAN8 and LGALS4 combination, displayed a sensitivity of 92.5% and a specificity of 67.2%. Our preliminary study was validated on a cohort of 134 subjects and it showed promising results for a prognostic test of blood screening. Nevertheless, it needs to be validated in a larger cohort with stage stratification and in patients with other gastrointestinal diseases.

Keywords: Colorectal cancer; blood biomarkers; FOBT; screening, mRNA

To cite this article: Maria Teresa Rodia et al. TSPAN8 and LGALS4 combination as blood biomarkers for colorectal cancer detection. Can Cell Microenviron 2016; 3: e1366. doi: 10.14800/ccm.1366.

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Introduction

To date, the creation of a screening test for the early detection of colorectal cancer represents an active field of investigation. According to the World Health Organization, the criteria for developing a screening test should include acceptability, practicability and high specificity and sensitivity [1].

By sampling one ml of whole blood, we propose a simple test, based on the abundance of two markers detected by qRT-PCR [2]. The panel of TSPAN8 and LGALS4 displayed a specificity of 67.2% and a sensitivity of 92.5%. These markers were discovered with a bio-informatics approach based on the Transcriptome Mapper (TRAM) [3], which allows a large-scale systematic meta-analysis of all available data sets of microarray experiments. The selection of the specific RNAs candidates was obtained by filtering for the genes that displayed the highest differential expression ratio between colorectal cancer tissue and normal blood samples. The computational analysis tested 38,104 human transcripts in 349 CRC and 200 blood samples.
The current state of the art

Current modalities for screening encompass the fecal occult blood test (FOBT) and sigmoidoscopy, which in Italy has a disappointing acceptance of 47% [4]. The currently elected test for FOBT is the Fecal Immunochemical Test (FIT). The FIT employs antibodies-based detection of human hemoglobin protein in the stool. The detection threshold for positivity is so far set at 100 nanograms per mL of globin levels, and with these parameters the calculated sensitivity is 73.8% and the specificity is 94.9% [5].

FOBT positivity is detected in about 1-5% of the tested population, and then requires further investigation by colonoscopy. Only 2% of FOBT positive subjects have colorectal cancer, while 20-30% have adenoma or polyps, diverticular disease, hemorrhoids, inflammatory bowel disease, etc. [6] Nevertheless, colonoscopy is the gold standard in terms of accuracy, sensitivity and specificity for investigating all types of bowel lesions. Of course, patient discomfort, the need for physician training and equipment [7] strongly encourage the search for additional non-invasive approaches.

To detect pre-neoplastic lesions, Imperiale et al., developed a multigetar stool DNA test in 2014, which was approved by the Food and Drug Administration (FDA) (Cologuard - Exact Sciences Corporation, Madison, WI). This test includes both quantitative molecular assays for KRAS mutations, aberrant NDRG4 and BMP3 methylation and β-actin, and a hemoglobin immunoassay (FIT). The sensitivity is impressively achieving 92.3% and specificity 86.6% [4].

Blood tests

Despite the systematic health promotion in organized screening programs the participation rates remain suboptimal. The reasons include the required, unappealing stool manipulation at home for the fecal occult blood test and the unpleasant bowel preparation required for colonoscopy. The main objective of screening could be, at first, to reach the 53% of the population that does not respond to the FOBT or sigmoidoscopy screening programs.

Unfortunately, the conventional blood-based tumour tests have failed to yield the necessary diagnostic accuracy for early detection, while proving complementary markers in treatment monitoring.

Carcinoembryonic antigen (CEA) is one of the first markers found for colorectal cancer detection [8]. Individuals with colorectal carcinoma often have higher levels of CEA in the blood than healthy individuals. The CEA blood test is not reliable as a screening test (sensitivity from 43 to 69 % and specificity from 70 to 95 % depending on the cut-off) [7] because high levels could be associated with several neoplastic or non-neoplastic pathologies. CEA measurement in blood is mainly used as a tumour marker to monitor colorectal carcinoma treatment, to identify recurrences after surgical resection, for staging or to localize cancer spread through measurement of biological fluids [9]. Peripheral blood monocytes could represent an interesting target of screening for their plasticity and versatility in response to microenvironmental stimuli. Hamm and colleagues identified the signature of 23 genes that might be used as a biomarker in CRC diagnosis and for the disease follow-up [10]. Peripheral blood mononuclear cells in combination with established plasma tumor markers constitute a novel blood test (Colox®) able to differentiate patients with CRC and adenomatous polyps from healthy individuals [11]. The test is based on a 29-gene panel expressed in peripheral blood mononuclear cell in combination with the protein tumor markers CEA and CYFRA21-2. It showed a specificity of 92.2% with a sensitivity for colorectal cancer and adenomatous polyps detection of 78.1% and 52.3%, respectively.

Furthermore, plasma-based DNA-markers have been evaluated, for example for genes with aberrant methylation such as the SEPT9 gene [12]. In April 2016, the FDA approved the first blood-based colorectal cancer screening test “Epi proColon” (sensitivity 48.2% and specificity 91.5%). Investigation into the long-term benefit of Epi proColon on colorectal cancer screening is currently ongoing.

Conclusions

Screening reduces mortality by 15-25%, but the hope is to improve these figures. As far as FIT is concerned, a new study proposed an improvement of the FIT increasing the cut-off level of detected hemoglobin and decreasing the times of screening [13], while the introduction of sDNA tests focused on the possibility of the early detection of precancerous lesions [5, 14, 15,16].

Due to their acceptability and lack of invasiveness, blood tests are the best candidate tests for regaining, first of all, the people that do not respond to screening programs. Several approaches have been attempted. So far, the markers are not specific enough [8] or the methods are too complex [10, 11].

Our proposed test, in this preliminary stage, represents a high degree of practicability with the association of good specificity and high sensitivity.

In the future, liquid biopsies could be earmarked for massive use from early detection to the identification of
treatments, like chemotherapy, after surgery. If more detailed studies confirm our result, the panel of markers that we propose could represent a valid tool for combination with the more common FIT. The association will improve the validity of the test by allowing better investigation also on precancerous adenomatous lesions.

**Conflicting interests**

The authors have declared that no conflict of interests exist.

**Abbreviations**

CRC: colorectal cancer; FOBT: fecal occult blood test; TRAM: Transcriptome Mapper.

**Author contributions**

M.R; R.S. and L.M, reviewed the literature and wrote the text.

**References**