The perturbation of fatty acids of erythrocyte membranes and blood serum in patients with colorectal cancer: new opportunities for diagnostics

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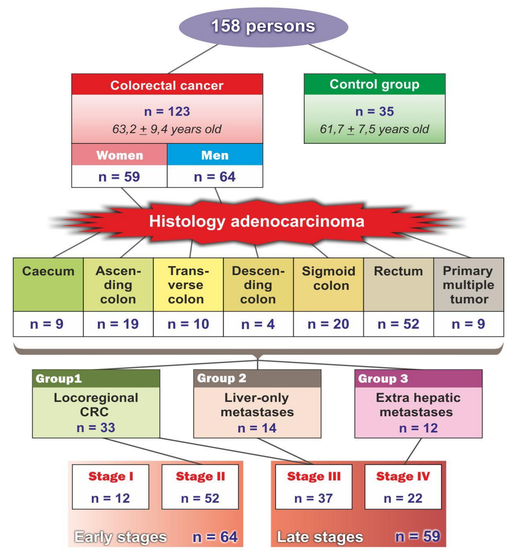
OBJECTIVES

Colorectal cancer (CRC) is the third most common cancer in the world. Clinical data show that 5-year survival rate of early-stage CRC postoperative patients is around 90%. However, most of CRC patients were diagnosed at advanced stage due to its asymptomatic and poor diagnostic techniques. Early screening is an effective way to reduce the morbidity and mortality. So, it is necessary to develop low-cost, less invasive, high-sensitivity, and high-specificity screening methods for early diagnosis of CRC and its progression.

The aim of the study was to investigate the perturbation of fatty acids (FA) of erythrocyte (RBC) phospholipid membrane and blood serum (BS) in order to find peculiarities which could be used for early screening, determination of progression of colorectal tumour of various localization and to reveal changing trends in CRC-related FA.

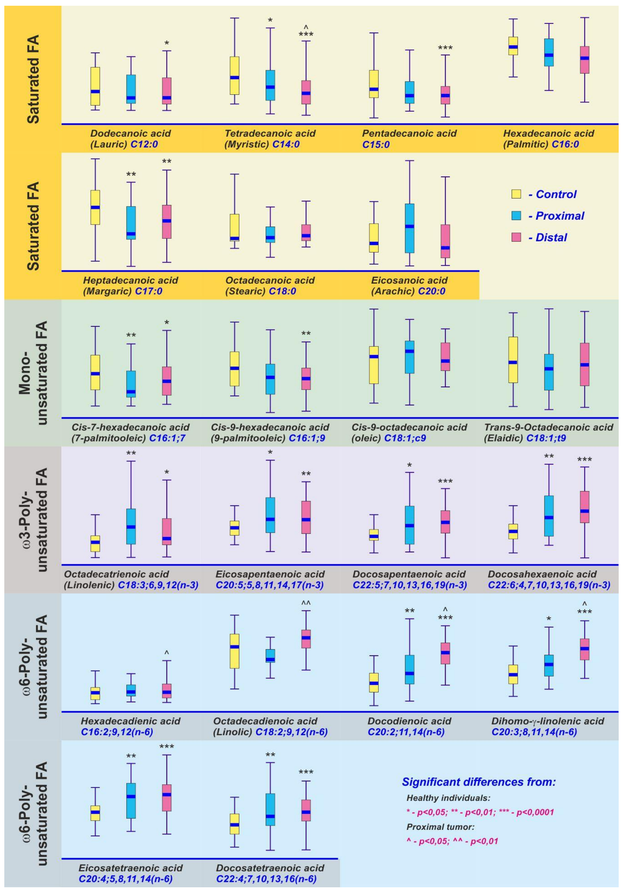
METHODS



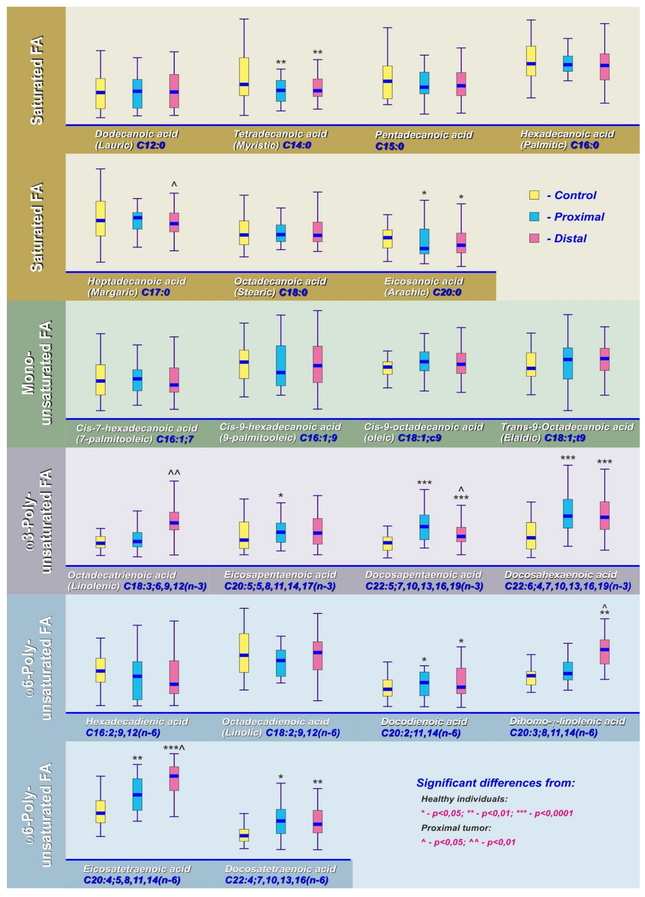
The CRC patients (63,2±9,4 years old) included 64 patients with early stage (TNM staging I, II), 59 with late stage (TNM staging III, IV) and various tumor locations. Late stage patients contain TNM staging III and IV with lymph node or distant metastases of various localizations (n=14 - liver-only, n=12 – extrahepatic). The healthy controls (n=35, 61,7±7,5 years old) were selected by routine clinical examination. RBC membrane and BS FA percentages were measured using GC/MS system triple quad Agilent 7000B (USA). Analysis was carried out by *Chenomex, MATLAB* software (Random Forest Classifier and PCA). FAs were identified using *Human Metabolic Data Base (HDMB)*.

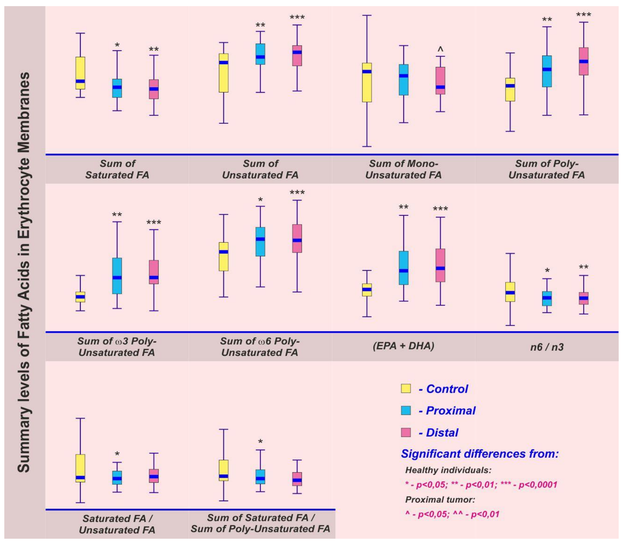
RESULTS

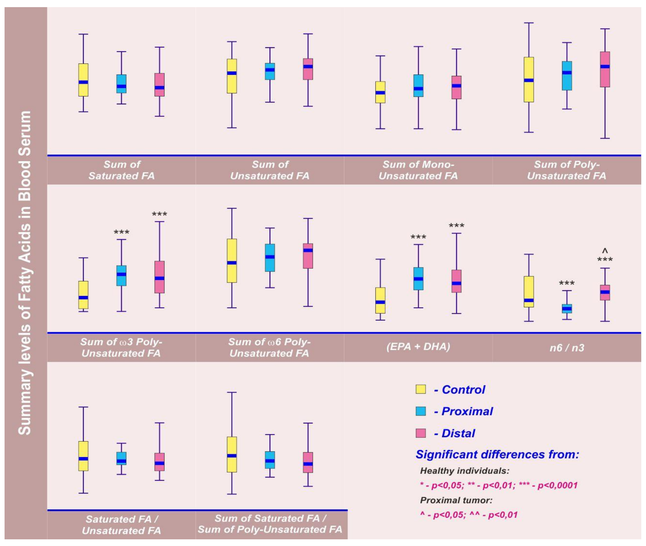
FA levels of RBC



FA levels of Serum

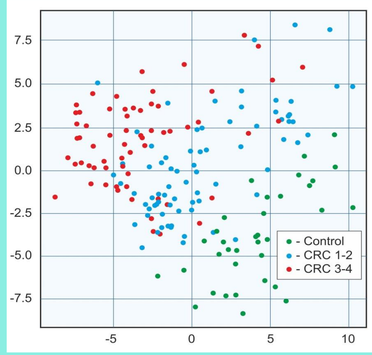




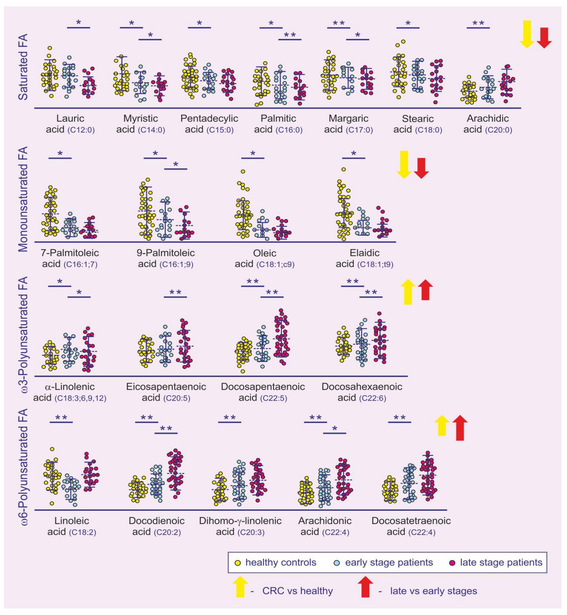


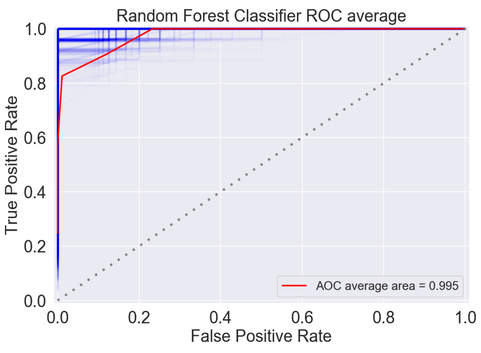
Significantly lower value of RBC C16:2 (p=0.015), C18:2 (p=0.004), C20:2 (p=0.011), C20:3 (p=0.025) and serum C18:3 (p=0.002), n-6/n-3 (p=0.04) as compared to distal tumour localization, has been noted for patients with proximal tumors. However the higher level of erythrocytes C18:1 (p=0.035), amount of MUFA (p=0.02) were observed in CRC patients with proximal tumors than those with distal. In patients with proximal tumours, lower mean level of RBC C20:5 (p<0.05) and serum C20:3 (p=0.04), C20:4 (p<0.05) as compared to patients with distal tumor were noted only for patients with disease progression.

Discriminated PCA results of RBC fatty acids data

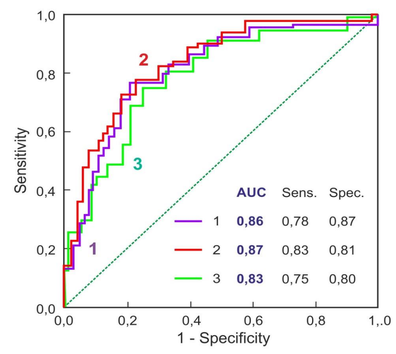


The main trends of the significant differentially expressed FAs between the CRC and healthy controls and between late and early stages of CRC





Random Forest Classifier application based on all data in database. 95 Features: Ctrl vs CRC (total).



Diagnostic accuracy evaluation using ROC curves for potential FA biomarkers:
Panel 1 - early stage CRC patients versus healthy controls;
Panel 2 - the late stage patients versus the early ones;
Panel 3 – the distant mts versus locoregional mts.

RESULTS & DISCUSSION

A total of 21 differentially expressed FA in RBC membrane and BS were identified. Each FA class demonstrated specific changing trends in CRC progression (down-regulation in saturated, monounsaturated (MUFA) and up-regulation in PUFA during cancer progression).
The revealed FA differences, associated with the stage of the disease, tumour localization served as the basis for development of diagnostic panels enabling to verify the CRC patients.
The panel 1 containing FA of RBC and BS: C20:2, C20:3, C20:4, C22:4, C22:5, C22:6 - achieved high diagnostic accuracy (0,79) with AUC of 0.86, a sensitivity of 0.78 and a specificity of 0.87 for differentiating early stage patients from healthy controls (OR 19,4 (0,17;0,55), which was better than the carcinoembryonic antigen biomarker [1]. The combination of two diagnostic panels, including RBC FA - C20:2, C20:3, C20:4, C22:4, C22:5, C22:6 and BS FA - C20:3, C20:4, C22:6 - showed the best predictive power when comparing the II stage CRC patients (AUC 0.82, diagnostic accuracy 0.81, sensitivity 0.73, specificity 0.86, OR 16.9) and III stage (AUC 0.84, diagnostic accuracy 0.80, sensitivity 0.76, specificity 0.86, OR 19.4) with healthy controls. The model 2 (FA of RBC - C 14:0, C16:0, C16:1, C18:1, C20:3, C20:4, C22:4, C22:5, C22:6) allowed us to determine the presence of distant metastases (AUC 0.83, OR=2.29). Probably, FA modifications are essential for correct signaling, including Hh, Wnt pathways, so perturbation of FA are closely associated with carcinogenesis [2, 3].

CONCLUSIONS

- A significant perturbation in the FA levels of RBC and BS associated with the presence of CRC, tumour location, its progression was found.
- Created FA panels showed good opportunities for distinguishing the early stage CRC patients from healthy controls - Panel 1 (AUC 0,86 (sens. 78, spec. 87), the early stage CRC patients from late ones - Panel 2 (AUC 0,87 (sens. 83, spec. 81), the distant metastasis versus locoregional mts - Panel 3 (AUC 0,83 (sens. 75, spec. 80).
- Created diagnostic panels, in which we took into account tumor localization, should be considered promising for early diagnosis, detection of CRC progression.

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