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Trefoil factor(s) and CA19.9: A promising panel for early detection of pancreatic cancer

Rahat Jahan [a], Koelina Ganguly [a], Lynette M. Smith [b], Pranita Atri [a], Joseph Carmicheal [a], Yuri Sheinin [c], Satyanarayana Rachagani [a], Gopalakrishnan Natarajan [a], Randall E. Brand [d], Muzafar A. Macha [a,e], Paul M. Grandgenett [g], Sukhwinder Kaur [a,*], Surinder K. Batra [a,f,g,**]

[a] Department of Biochemistry and Molecular Biology, College of Medicine, University of Nebraska Medical Center, Omaha, NE 68198-5870, USA
[b] Department of Biostatistics, College of Public Health, University of Nebraska Medical Center, Omaha, NE 68198-5870, USA
[c] Department of Pathology and Microbiology, College of Medicine, University of Nebraska Medical Center, Omaha, NE, USA
[d] Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
[e] Department of Otolaryngology-Head & Neck Surgery, College of Medicine, University of Nebraska Medical Center, Omaha, NE 68198-5870, USA
[f] Buffett Cancer Center, University of Nebraska Medical Center, Omaha, NE, USA
[g] Eppley Institute for Research in Cancer and Allied Diseases, University of Nebraska Medical Center, Omaha, NE, USA

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ABSTRACT

Background: Trefoil factors (TFF1, TFF2, and TFF3) are small secretory molecules that recently have gained significant attention in multiple studies as an integral component of pancreatic cancer (PC) subtype-specific gene signature. Here, we comprehensively investigated the diagnostic potential of all the member of trefoil family, i.e., TFF1, TFF2, and TFF3 in combination with CA19.9 for detection of PC.

Methods: Trefoil factors (TFFs) gene expression was analyzed in publicly available cancer genome datasets, followed by assessment of their expression in genetically engineered spontaneous mouse model (GEM) of PC (KrasG12D; Pdx1-Cre (KC)) and in human tissue microarray consisting of normal pancreas adjacent to tumor (NAT), precursor lesions (PanIN), and various pathological grades of PC by immunohistochemistry (IHC). Serum TFFs and CA19.9 levels were evaluated via ELISA in comprehensive sample set ($n = 362$) comprised of independent training and validation sets each containing benign controls (BC), chronic pancreatitis (CP), and various stages of PC. Univariate and multivariate logistic regression and receiver operating characteristic curves (ROC) were used to examine their diagnostic potential both alone and in combination with CA19.9.

Findings: The publicly available datasets and expression analysis revealed significant increased expression of TFF1, TFF2, and TFF3 in human PanINs and PC tissues. Assessment of KC mouse model also suggested upregulated expression of TFFs in PanIN lesions and early stage of PC. In serum analyses studies, TFF1 and TFF2 were significantly elevated in early stages of PC in comparison to benign and CP control group while significant elevation in TFF3 levels were observed in CP group with no further elevation in its level in early stage PC group. In receiver operating curve (ROC) analyses, combination of TFFs with CA19.9 emerged as promising panel for discriminating early stage of PC (EPC) from BC ($AUC_{TFF1+TFF2+TFF3+CA19.9} = 0.93$) as well as CP ($AUC_{TFF1+TFF2+TFF3+CA19.9} = 0.93$). Notably, at 90% specificity (desired for blood-based biomarker panel), TFFs combination improved CA19.9 sensitivity by 10% and 25% to differentiate EPC from BC and CP respectively. In an independent blinded validation set, the combination of TFFs and CA19.9 ($AUC_{TFF1+TFF2+TFF3+CA19.9} = 0.82$) also improved the overall efficacy of CA19.9 ($AUC_{CA19.9} = 0.66$) to differentiate EPC from CP proving unique biomarker capabilities of TFFs to distinguish early stage of this deadly lethal disease.

Interpretation: In silico, tissue and serum analyses validated significantly increased level of all TFFs in precursor lesions and early stages of PC. The combination of TFFs enhanced sensitivity and specificity of CA19.9 to discriminate early stage of PC from benign control and chronic pancreatitis groups.

Abbreviations: TFF1, Trefoil Factor 1; TFF2, Trefoil Factor 2; TFF3, Trefoil Factor 3; CA19.9, Cancer Antigen 19.9; AUC, Area under the ROC curve; SN, Sensitivity; SP, Specificity; ROC, Receiver Operating Curve; PC, Pancreatic Cancer; BC, Benign Cancer; CP, Chronic Pancreatitis; EPC, Early Pancreatic Cancer; LPC, Late Pancreatic Cancer.

* Correspondence to: S. Kaur, Department of Biochemistry and Molecular Biology, University of Nebraska Medical Center, 985870, Nebraska Medical Center, Omaha, NE, 68198-5870, USA.

** Correspondence to: S. K. Batra, Department of Biochemistry and Molecular Biology, Eppley Institute for Research in Cancer and Allied Diseases, University of Nebraska Medical Center, 985870, Nebraska Medical Center, Omaha, NE 68198-5870, USA.

E-mail addresses: skaur@unmc.edu (S. Kaur), sbatra@unmc.edu (S.K. Batra).

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