

## Is Alpha-1 Antitrypsin a Potential Tumor Biomarker in Colorectal Cancer? Comment on: “Jaberie H., et al. Evaluation of Alpha1-Antitrypsin for the Early Diagnosis of Colorectal Cancer. *Pathol Oncol Res* 2019

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### Abbreviations

AAT: Alpha-1 Antitrypsin; CEBM: Centre for Evidence-Based Medicine; CEA: Carcinoembryonic Antigen; CRC: Colorectal Cancer; g/L: Grams Per Litre; HUCA: University Central Hospital of Asturias, Oviedo (Asturias, Spain); min/ml: Minute Per Millilitre; ng: Nanograms; p: Statistical value that implies significance when  $< 0,05$ ; Pi\*MM: Protease Inhibitor MM Genotype; ROC Curve: The Receiver Operating Characteristic Curve

### Background

Human alpha-1 antitrypsin (AAT), also called alpha-1 proteinase inhibitor and SERPINA1 (serine protease inhibitor, clade A, member 1), is a serine protease inhibitor with anti-inflammatory, anti-apoptotic, and immunomodulatory properties. Human AAT is primarily synthesized and secreted by hepatocytes (> 80%), and in additional quantities by monocytes, macrophages, alpha and delta cells of pancreas, type II alveolar epithelial lung cells, enterocytes, keratinocytes, and cancer cells from adenocarcinomas, sarcomas, glioblastomas and chordomas. As an acute phase reactant, AAT plasma levels increase in response to inflammatory or infectious stimuli, accompanying C-reactive protein and serum amyloid A. Serum levels are also slightly increased by the use of contraceptives and during pregnancy [1].

The relationship between AAT serum concentration and Colorectal Cancer (CRC) is controversial. On the one hand, higher levels of AAT concentrations has been reported in CRC patients compared to healthy controls [2] and on the other some clinical studies have shown that, providing a very weak evidence (3a/3b level of evidence according to the Oxford CEBM guidelines) subjects with deficiency of AAT could have an increased risk of developing CRC [3].

And although, the AAT serum level has been contemplated as a potential tumour biomarker, its role in cancer biology remains unknown.

### Comments

This topic has been recently analysed by Jaberie H., *et al* [4]. In order to investigate a biomarker for the early diagnosis of CRC, the authors studied a total of 113 patients suffering CRC, 86 out of 113 patients underwent tumour resection, and were compared to 50 healthy controls. All participants had a normal Pi\*MM genotype. The mean and ranges of plasma Carcinoembryonic Antigen (CEA) and AAT were analysed in both groups, taking into account several conditions, such as: age, gender, tumour size (smaller or greater than 5 cm), location (right/left sided), surgery stage (I to IV), and cellular differentiation (well, moderate, poor).

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Although the small sample size of the study may inevitably lead to biases that would limit the study conclusions, their results showed significant differences in AAT concentration between large tumours compared to the smaller ones (2.73 vs. 2.15 g/L;  $p = 0.0001$ ). As expected [2], authors found that the mean serum levels of AAT were significantly higher in patients with CRC (mean 2.34 g/L) than in healthy controls (mean 1.4 g/L;  $p = 0.0001$ ). In addition, the CRC cases in advanced stages had higher AAT serum concentrations than those in early stages ( $p < 0.014$ ), but no differences were found related to the location of the tumours. By measuring the activity of the AAT (expressed as micromol/min/mL) and the ROC curve (i.e. the receiver operating characteristic curve), the cut-off point suggested by the authors, was 1.88 g/L, with a sensitivity of 75.2% and a specificity of 90%. These results seemed to be better than, at the authors discretion, using a CEA cut-off point of 3.56 ng/ml: 70.8% and 70%, respectively.

To explain the increase of AAT levels in blood of CRC subjects, the authors suggest that the tumour cells themselves may contribute to the protein secretion, although the increased synthesis of AAT by immigrants leukocytes to the inflammatory focus in response to pro-inflammatory mediators released by inflamed tissues could also contribute to this phenomenon [1].

Therefore, despite the promising results provided by the Jaberie's., *et al.* Study [4], the small sample size and some limitations inherent to the fact that AAT is an acute phase reactant whose serum concentrations are not constant and have a range very broad [1-3], more studies designed with larger samples would be needed to reach more precise conclusions.

### **Competing Interests**

The authors declare that they have no competing interests.

### **Authors Contributions**

Dr SPH reviewed the original manuscript, reinterpreted the data and contributed to the final writing of the present comment. Dr IB participated in the analysis of the paper and approved its final version.

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