Gastroenterol Hepatol. 2016;39(7):433–441

Gastroenterología y Hepatología

www.elsevier.es/gastroenterologia

ORIGINAL ARTICLE

Plasma matrix metalloproteinase 9 as an early surrogate biomarker of advanced colorectal neoplasia

Antonio Z. Gimeno-García[a,*], Javier Triñanes[d], Enrique Quintero[a,c], Eduardo Salido[b,c,d], David Nicolás-Pérez[a], Zaida Adrián-de-Ganzo[a], Onofre Alarcón-Fernández[a], Beatriz Abrante[a], Rafael Romero[a], Marta Carrillo[a], Laura Ramos[a], Inmaculada Alonso[a], Juan Ortega[a,b,c,d], Alejandro Jiménez[d]

[a] *Gastroenterology Department, La Laguna University, Tenerife, Spain*
[b] *Pathology Department, La Laguna University, Tenerife, Spain*
[c] *La Laguna University, Tenerife, Spain*
[d] *Research Unit, Hospital Universitario de Canarias, Tenerife, Spain*

Received 19 July 2015; accepted 1 October 2015

KEYWORDS
Matrix metalloproteinases;
Colorectal cancer;
Advanced adenoma;
Plasma biomarker;
Gelatin zymography

Abstract
Introduction: Matrix metalloproteinases (MMPs) are overexpressed at different stages of colorectal carcinogenesis and could serve as early surrogate biomarkers of colorectal neoplasia.
Objective: To assess the utility of plasma MMP2 and MMP9 levels in the detection of advanced colorectal neoplasia and their correlation with tissue levels.
Methods: We analysed blood and tissue samples from patients with non-advanced adenomas ($n = 25$), advanced adenomas ($n = 25$), colorectal cancer ($n = 25$) and healthy controls ($n = 75$). Plasma and tissue gelatinase levels were determined by Luminex XMAP technology and gelatin zymography. Receiver operating characteristic (ROC) curve analysis was used to calculate the optimum cut-off for the detection of advanced colorectal neoplasia.
Results: Plasma MMP2 levels were similar between groups whatever the type of lesion. Plasma MMP9 levels were significantly higher in patients with neoplastic lesions than in healthy controls (median 292.3 ng/ml vs. 139.08 ng/ml, $P < 0.001$). MMP9 levels were also higher in colorectal cancer than in non-advanced adenomas (median 314.6 ng/ml vs. 274.3 ng/ml, $P = 0.03$). There was a significant correlation between plasma and tissue levels of MMP9 ($r = 0.5$, $P < 0.001$). The plasma MMP9 cut-off range with the highest diagnostic accuracy was between 173 ng/ml and 204 ng/ml (AUC = 0.80 [95% CI: 0.72–0.86], $P < 0.001$; sensitivity, 80–86% and specificity, 57–67%).

* Corresponding author.
E-mail address: antozeben@gmail.com (A.Z. Gimeno-García).

Conclusion: Plasma MMP9 could be a surrogate biomarker for the early detection of advanced colorectal neoplasia, although its diagnostic performance could be increased by combination with other biomarkers.

PALABRAS CLAVE
Metaloproteinasas;
Cáncer colorrectal;
Adenoma avanzado;
Biomarcadores en plasma;
Zimografía con gelatina

Metaloproteinasa 9 como biomarcador plasmático de neoplasia colorrectal avanzada

Resumen
Introducción: Las metaloproteinasas (MMP) son proteínas que se sobreexpresan en diferentes etapas de la carcinogénesis colorrectal y podrían ser biomarcadores de neoplasia colorrectal.
Objetivo: Evaluar la utilidad de MMP2 y MMP9 en plasma para detectar neoplasia colorrectal avanzada y su correlación con los niveles tisulares.
Métodos: Se analizaron muestras de sangre y tejido en pacientes con adenomas no avanzados ($n = 25$), adenomas avanzados ($n = 25$), cáncer colorrectal ($n = 25$) y controles sanos ($n = 75$). Los niveles plasmáticos y en tejido se determinaron mediante tecnología xMAP Luminex y zimografía con gelatina. Se utilizaron curvas ROC para calcular el punto de corte óptimo para neoplasia colorrectal avanzada.
Resultados: Los niveles de MMP2 fueron similares en las distintas lesiones. Los niveles de MMP9 fueron significativamente superiores en los pacientes con lesiones neoplásicas comparados con controles sanos (mediana de 292,3 ng/ml vs. 139,08 ng/ml; $p < 0,001$). Los niveles de MMP9 fueron más altos en los cánceres colorrectales que en adenomas no avanzados (mediana de 314,6 ng/ml vs. 274,3 ng/ml; $p = 0,03$). Se observó correlación entre los niveles plasmáticos y tisulares de MMP9 ($r = 0,5$; $p < 0,001$). El rango de MMP9 plasma con mayor precisión diagnóstica fue 173–204 ng/ml (AUC = 0,80 [IC 95%: 0,72–0,86], $p < 0,001$; sensibilidad 80–86% y especificidad 57–67%).
Conclusión: Los niveles en plasma de MMP9 podrían ser un biomarcador útil para detectar neoplasia colorrectal avanzada. La combinación con otros biomarcadores podría aumentar su rendimiento diagnóstico.

Introduction

Matrix metalloproteinases (MMPs) are a multigene family of zinc-dependent extracellular matrix (ECM) proteases that play an important role in tissue remodelling. Although they have been implicated in the pathogenesis of various inflammatory diseases,[1] they are also involved in different stages of carcinogenesis including ECM degradation associated with tumour growth and angiogenesis, local invasion and extravasation.[2] In fact, MMPs are considered the most important factors involved in ECM remodelling, capable of creating a pathway for tumour cells.[3]

The type IV collagenases, MMP2 (gelatinase A) and MMP9 (gelatinase B), have been extensively studied in epithelial tumours and their expression has been related to the breakdown of the first barrier against invasion, the basement membrane, which has been associated with a high frequency of distant metastasis.[4] Both gelatinases also play an important role in the development of the angiogenic phenotype.[5,6]

In colorectal cancer (CRC), high levels of gelatinases have been associated with increased risk of metastatic disease and poor survival rates.[7–10] Several studies have demonstrated overexpression of these enzymes in tissue samples of CRC compared with colorectal adenomas or normal tissue.[11,12] Other studies have shown increased levels of gelatinases in serum and plasma of patients with CRC compared with healthy controls (HC), and are considered as potential diagnostic biomarkers.[13–16] However, most studies carried out in blood samples have focused on advanced disease[13,15] or on testing the usefulness of gelatinase levels as prognostic biomarkers of recurrence after surgery,[17,18] but not their potential role in the detection of early stages of CRC (advanced adenoma and carcinoma). In addition, data on gelatinase levels in blood samples as diagnostic biomarkers are scarce and inconsistent between studies.[13,14,19,20] Some studies have found an association between certain polymorphisms and the risk of CRC, but the results are not conclusive.[21,22] The promoter variant of MMP9, −1562C>T, has been the most extensively studied with contradictory results.[21,23,24] The genotype 279R>Q has been associated with early CRC.[22]

In the current study we hypothesized that MMP2 and or MMP9 may be upregulated in both tissue and plasma samples of patients with advanced colorectal neoplasia, and that elevated gelatinase plasmatic levels could be useful as an early surrogate biomarker of advanced colorectal neoplasia.

The aim of the present study was to assess plasma gelatinase levels in the early stages of the colorectal