Prognostic Role of Tissue Factor in Hepatocellular Carcinoma

Evaluation of plasmatic Tissue Factor in patients affected by Hepatocellular Carcinoma

Abstract

The Hepatocellular Carcinoma (HCC) is the fifth most common cancer worldwide, with poor prognosis. Due to the important role of the liver in blood coagulation, acute and chronic liver diseases as well as HCC are associated with disorders ranging from bleeding to thrombosis.

Tissue Factor (TF) is a protein circulating in plasma in two main isoforms: a transmembrane full-length form, known to trigger the blood coagulation, and a soluble form, due to an alternative splicing (TFs) with unclear functions. TF isoforms are constitutively expressed in a variety of tumor cells. To study the expression of TF in the HCC and its potential involvement, plasma samples from HCC patients were investigated by means of antigenic and activity assays.

Preliminary data analysis showed that total TF has an elevated concentration in HCC patients. Since the full-length TF (FL-TF) levels were found in the normal range, as-TF could be the isoform responsible for the increased levels of total TF. However, it was not found any statistically significant correlation between TF levels and the activation of coagulation markers.

Further evaluation of TF levels in relation to the patient clinical data will give additional insight to understand more the relationship between TF and HCC evolution.

Introduction

Hepatocellular Carcinoma (HCC) accounts for 80-90% of liver cancers and develops from malignant transformation of hepatocytes, one of the predominant and most important cell types of the liver. HCC is the fifth most common cancer worldwide, one of the most aggressive, and the second leading cause of cancer mortality. In 2008, there were 749,000 new cases and 695,000 deaths from liver cancer, which increased to 782,000 new cases in 2012.

Aims and questions

The aim of this study is to evaluate if there is a relationship between the expression of several isoforms of TF in plasma and the HCC evolution. In particular, this study will focus on the investigation of the questions:

1. Is plasmatic TF level increased in HCC patients?
2. Does TF level correlate with coagulation activation markers such as D-dimers and thrombin-antithrombin complexes?

Discussion

This study presents for the first time an evaluation of circulating TF levels and global indicators of blood coagulation activators and inhibitors (D-dimers, TAT) in HCC patients and indicates that total TF has an elevated concentration in HCC patients. Since the full-length TF levels were found in the normal range, as-TF could be the isoform responsible for the increased TF levels. However, the increased level of TF were not statistically correlated to the activation of blood coagulation markers. Further evaluation of TF levels in relation to the patient clinical data will give additional insights to understand more the relationship between TF and HCC evolution.

References


Material and methods

Patients and sample collection

A total of 80 patients were selected from a database belonging to the Swiss Group for Clinical Cancer Research (SAKK). In particular, the database (SAKK 77/08 and 77/09) includes biological samples from patients with HCC before and after immunosuppressive treatments (e.g. Everolimus/Sorafenib). For each patient, blood was collected in 3.2% sodium citrate tubes and centrifuged within 2 hours of collection at room temperature and 2700×g for 10 minutes in order to obtain plasma. To avoid the presence of patients’ cellular debris, the plasma was centrifuged again for 10 minutes at 1500×g and then stored at -80°C.

Methods

To evaluate the TF levels in plasma, three different commercial kits capable of measuring TF full-length, total TF (full-length and alternative) and TF-associated with MPs were used. To date, it does not exist either an antigenic test or an activity test that allows the specific measurement of as-TF. In addition, to evaluate the risk of thrombosis or the presence of thrombotic events, D-dimers, thrombin-antithrombin complex (TAT) levels were measured.

Results

1. Is plasmatic TF level in HCC patients? Which are the most affected isoforms?

2. Does TF level correlate with coagulation activation markers such as D-dimers and thrombin-antithrombin complexes?