Institution för Laboratorimedicin

Prevention of liver cancer in chronic liver disease: An experimental study of sodium selenite and rat hepatocarcinogenesis

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Suvd Erkhembayar
MD

Huvudhandledare:
Professor Lennart Eriksson
Karolinska Institutet
Institutionen för laboratorimedicin,
Avdelningen för patologi

Bihandledare:
Professor Mikael Björnstedt
Karolinska Institutet
Institutionen för laboratorimedicin,
Avdelningen för patologi

Betygsnämnd:
Professor Joseph de Pierre
Stockholm Universitet,
Institutionen för Biokemi och Biofysik

Adjungerad professor Moustapha Hassan
Karolinska Institutet,
Institutionen för laboratoriemedicin

Professor Agneta Mode
Karolinska Institutet,
Institutionen för biovetenskaper och näringslära (Bionut), H2

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ABSTRACT

Selenium treatment in supranutritional but subtoxic doses has previously been shown to inhibit cell proliferation in preneoplastic lesions in a rat liver carcinogenesis model. The mechanisms are not known, but thioredoxin reductase (TrxR1), a seleno-enzyme essential for maintaining intracellular redox status and cellular defence against oxidative stress might be involved. The aim of this work was to study whether selenium affected regenerative liver growth after partial hepatectomy as it did neoplastic growth and to study the effect of selenium on TrxR1 expression and regulation in regenerative and normal rat liver. To address these questions, we have compared the effect of sodium selenite on tumour growth in an experimental rat liver model for the development of hepatocellular carcinoma with the effect of sodium selenite on regeneration of liver mass after 2/3 partial hepatectomy and the effect of 10 weeks sodium selenite treatment on normal rats.

Sodium selenite administered in the drinking water (5µg/ml) reduced the rate of tumour growth during progression up to 12 months after initiation, but it did not affect gain of liver mass or rate of cell proliferation up to three weeks after 2/3 partial hepatectomy. Sodium selenite supplementation at dose levels of 1µg/ml and 5µg/ml showed an initial dose dependent increase of blood and liver levels of selenium. At 6 and 8 weeks, respectively, the selenium concentrations equilibrated regardless of dose and with no further accumulation. Sodium selenite did not affect body weight or relative liver mass at given doses.

We also explored whether TrxR1 was a marker of the liver tumour phenotype or if the TrxR1 over expression found in liver preneoplasia and neoplasia could be explained only by TrxR1 induction in growing cells. We found that from 6 months after initiation in the tumour model TrxR1 was only expressed in neoplastic liver lesions that showed signs of cell proliferation (bromodeoxyuridine (BrdU) incorporation), while remodelling preneoplastic liver nodules that were BrdU negative were immunohistochemically negative for TrxR1. Both types of lesions were, however, expressing the classical marker of preneoplastic and neoplastic nodules, glutathione S-transferase π (GST-π). During liver cell regeneration TrxR1 was induced at the time of cell proliferation, but was back to background activity 72 hours after partial hepatectomy. Sodium selenite potentiated this increase in enzyme activity. When sodium selenite was given to normal rats over long time TrxR1 activity was induced in the liver to an extent reflecting the liver selenium levels. TrxR1 mRNA was, however, only increased over background at the time when the selenium level was increasing. We found that, although TrxR1 did increase to a certain extent during cell proliferation, the neoplastic over expression of TrxR1 was not correlated to the rate of cell growth in the tumours. Our interpretation of the finding that TrxR1 was selectively over expressed in the growing preneoplastic and neoplastic liver lesions is that TrxR1 is a tumour marker with a higher specificity to neoplasia with an increased risk for malignant transformation.

Based on the facts that long-term treatment of selenite did not cause accumulation of selenium or selenium toxicity and the fact that selenium inhibited only neoplastic growth but not regenerative growth we suggest that selenium is a suitable candidate for tumour prevention in patients with chronic liver disease dependent on sustained ability of liver regeneration. Furthermore TrxR1 is a histological marker in chronic liver disease for liver cancer and liver cancer prestages with a potential to be a marker for liver cancer risk.

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