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Investigations of trace elements in metastases and primary carcinoma of the prostate

A. Feustel[1], R. Wennrich[2], and H. Dittrich

[1] Department of Urology, Markkleeberg Hospital, Leipzig, and
Departments of [2]Chemistry and [3]Veterinary Medicine, Karl-Marx-University, Leipzig, German Democratic Republic

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Summary. The concentration of several trace elements (Cd, Zn, Mn, Cr, Pb, Se) as determined both in primary prostatic carcinoma and in metastases of the same patients in unseparated and in separated tissue. In the unseparated tissue a significantly higher amount of all elements studied was found in the primary tumour. Different results were obtained for the concentrations in separated epithelium and stroma as well as in the cellular fractions of metastases and of primary tumour.

Key words: Prostate cancer – Metastases – Cellular fractions – Epithelium and stroma – Trace elements

Introduction

Prostate cancer metastasises widely. There is a high prevalence of prostate cancer post mortem which in most cases does not become clinically manifest. The high mortality rate may be related to the fact that about 80% of prostatic cancer patients first present with evidence of metastases. A special model is needed to investigate the properties of prostate cancer about which, in comparison with other forms of cancer, little is known.

Previous studies showed an antagonistic biological effect with Zn and Cd in the prostatic gland. We found an increased content of Zn in BPH and a decrease of this element in prostatic cancer compared to normal prostatic tissue. There was also a continous increase of Cd concentration from normal prostate through BPH to carcinoma [1]. These results were confirmed by the identification of these trace elements in the cellular fractions of the same material [2]. In agreement with the results obtained by Habib [3] we confirmed the general decrease of the Zn concentration from BPH to prostatic carcinoma both in epithelium and stroma [4].

We decided to investigate the concentration of several trace elements in both the primary tumor and in the metastases from the same patient. The investigations were done with cellular fractions of the prostatic carcinoma and of the metastases. Additionally the concentration of zinc, cadmium, selenium, magnesium, lead and chromium were measured in separated epithelium and stroma of the primary and secondary tumor.

Materials and methods

Pieces of histologically proven prostate cancer and metastases were taken from 5 patients. Additionally primary tumour tissue of 11 prostatic cancer patients were investigated. One part of each sample was taken for separation into epithelial and stromal portions. A second part was used for the preparation of cellular fractions. The separation of epithelium and stroma was effected by collagenase (SERVA) in a Krebs-Ringer-buffer at 37°C for 1 h. The epithelial cells were separated from the stromal solution by centrifugation (15 min, 800 g) [4].

The preparation of cellular fractions was made in a Potter homogenizer made from PTFE. The subsequent subcellular fractionation was achieved by centrifuging prostate tissue homogenates [2].

All fractions were dried and wet ashed by nitric acid. The trace elements were analyzed by atomic emission spectrometry with inductively coupled plasma (Spectroflame, Spectro Kleve, FRG) or flameless atomic absorption spectrometry (VEB Carl-Zeiss Jena, GDR). Selenium was analyzed with hydride generation atomic absorbtion spectrometry.

Results

In both cellular fractions and in the unseparated tissue from metastases we recorded the concentration of Cd, Zn, Se, Mn and Pb. The results are given in Table 1.

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Table 1. Concentration of several elements in cellular fractions of metastases (ppm). $n = 4$

	Cellular fraction			Unseparated
	nuclear	mitochondrial	cytosol	
Cd	0.16 ± 0.10	0.09 ± 0.01	0.11 ± 0.10	0.12 ± 0.10
Zdn	26 ± 13	36 ± 2	31 ± 30	39 ± 12
Se	1.3 ± 1.0	1.9 ± 0.8	0.23 ± 0.18	1.5 ± 0.3
Mn	3.6 ± 3.0	3.7 ± 1.8	0.51 ± 0.26	3.9 ± 0.5
Pb	23 ± 22	12 ± 9	10 ± 7	120 ± 12

Table 2. Relationship of the concentration of trace elements in cellular fractions an unseparated tissue of prostatic carcinoma and metastatis of the same patient. $n = 4$

Element	Cellular fraction			
	nuclear	mitochondrial	cytosol	unseparated tissue
Cd	0.78 ± 0.41	2.8 ± 1.8	4.6 ± 1.8	4.3 ± 2.0
Zn	5.9 ± 3.6	6.4 ± 3.2	7.3 ± 3.2	4.4 ± 2.7
Se	5.1 ± 3.7	1.2 ± 0.2	0.63 ± 0.37	3.5 ± 2.5
Mn	1.6 ± 1.5	0.7 ± 0.2	2.2 ± 1.4	1.8 ± 0.3
Pb	2.9 ± 2.4	3.4 ± 2.2	1.9 ± 1.0	1.9 ± 0.8

Table 3. Relationship of the concentration of trace elements in separated epithelium to stroma in primary tumours and metastases

	Cd	Zn	Se	Cr	Mn
Prostatic carcinoma ($n = 11$)					
Epithelium					
stroma	3.8	11[a] 1.7[b]	2.8	9.4	10
Metastases of patients with prostatic CA ($n = 3$)					
Epithelium					
stroma	23	17	n.d.	21	36

[a] poorly diff. carcinoma
[b] well diff. carcinoma
n.d. = not detectable

Table 4. Relationship of trace element concentrations in separated epithelium and stroma of prostatic CA and metastases of the same patients

Element	Concentration prostatic CA/metastases	
	epithelium	stroma
Cd	0.64 ± 0.21	0.96 ± 0.25
Zn	0.47 ± 0.16	0.66 ± 0.13
Se	values in metastases not detectable	
Mn	0.73 ± 0.03	1.47 ± 0.76
Cr	0.38 ± 0.06	1.43 ± 1.07

There were no significant differences in the concentration of Cd and Zn in all cellular fractions from metastases.

Compared to this we had found decreased Zn-concentrations in the nuclear fraction of poorly - differentiated primary carcinoma [2]. The concentration of selenium and manganese was decreased in the cytosol of metastases.

In metastases we also found differences in the concentration of lead between the unseparated material and the cellular fractions. We assumed that the greater proportion of this element was not cell bound.

The relationship of the concentration of trace elements between the primary tumor and the metastases in the same patients is given in Table 2.

We obtained in the unseparated tissue in all cases significantly higher amounts in the primary tumor tissue than in metastases. This relationship was reflected for the concentration of zinc and lead in all fractions compared.

Table 5. Conclusion

• Trace elements in metastases	
Cd, Zn, Mn, Cr:	epithelium > stroma
Se:	not detectable
• Trace elements in primary tumour	
Cd, Zn, Se, Mn, Cr:	epithelium > stroma
• Trace elements in prostatic carcinoma > metastases	
Zn, Se, Mn, Pb:	in nuclear fraction
Cd, Zn, Se, Pb:	in mitochondrial fraction
Cd, Zn, Mn, Pb:	in cytosol
• Trace elements in metastases > prostatic carcinoma	
Cd:	in nuclear fraction
Cr, Mn:	in stroma
Cd, Zn, Mn, Cr:	in epithelium

In view of a possible inhibitory role of selenium in chemical carcinogenesis we found a distinct decrease of this metal bund in metastases compared with the primary tumor.

The results obtained in separated epithelium and stroma from primary tumour and metastases are given in Table 3.

These results show that the metals were generally increased in the epithelium.

In the primary tumors we found distinct differences in the concentration of zinc between well and poorly – differentiated carcinoma. The Zn – concentration was decreased in the epithelial fraction of poorly – differentiated carcinoma compared with the well – differentiated lesions.

The relationship of the Zn-values between epithelium and stroma was increased in poorly differentiated tumors.

In the metastases of the same patients we also found significantly higher metal concentration in the epithelium. It was interesting that selenium was not found in detectable amounts.

The comparison of the relationship of trace elements in epithelium and stroma between the primary tumor and the metastases are given in Table 4.

The values showed that the concentration of Cd, Zn, Mn and Cr in the epithelium of metastases was increased in comparison to the epithelium of the primary tumour. We could not find a well defined trend in the level of trace elements investigated in the stromal fractions compared.

Conclusions

Systematic studies are required to determine the biological factors associated with the different tumor types and to determine the metastatic potential of prostate cancer. With this first investigation of trace elements in metastases and in primary tumor of the prostate we looked for a possible interaction between prostate cancer cells and the extracellular components including the stromal elements. The results are summarized in Table 5.

Both in the primary tumor and the metastases we found a higher concentration of the elements in the epithelium than in stroma. Most of the elements are increased in the epithelial fraction of metastases compared with the prostatic carcinoma. In the cellular fraction of the primary tumors we obtained higher concentration of these metals than in metastases. Selenium was not detectable in metastases.

This study of the trace elements in tissues of prostate cancer and metastases could characterize the factors which determine the organ patterns of metastases and the primary tumor.

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Prof. Dr. A. Feustel
Abteilung für Urologie
Krankenhaus Markkleeberg
Pfarrgasse 15
GDR-7113 Markkleeberg
German Democratic Republic