Prostanoids and metastases in facial tumors


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INTRODUCTION

Beside the well known biological functions (mediators in inflammation and immune regulation) there is some evidence that metabolites of arachidonic acid play a role in tumor growth and metastases (1, 2).

Matejka et al. (8) reported about relations between the occurrence of the stable arachidonic metabolite 6-keto-PGF$_{1\alpha}$ in plasma and tumor metastases.

In oral squamous cell carcinomas Schultz et al. (4) found higher prostacyclin synthesis activities in tumor surrounding skin than in tumor tissue.

In opposite to the clinical importance there are only limited knowledges about the reasons of different synthesis rates of arachidonic acid metabolites in tumor tissue and in clinical healthy skin.

In our patients (n=96) with tumors we measured the stable final products 6-keto-prostaglandin F$_{1\alpha}$ (6-oxo-PGF$_{1\alpha}$) and thromboxane B$_2$ (TXB$_2$) in standardized punch biopsies (ø 4mm) in comparison to the surrounding clinically healthy tissue.

Figure 1. Metabolic pathways of arachidonic acid
MATERIALS AND METHODS

Materials and methods are shown in figure 2.

Punch biopsies (ø 4 mm) (Tumor vs surrounding healthy skin, mucosa)

Washing in NaCl (0,9 %)

Incubation in Tyrode-solution (37°C)

TXB₂ und 6 - oxo - PGF₁α - ELISA

0,2 ml/well TXB₂ / 6 - oxo - PGF₁α - antiserum in carbonate buffer pH 9,6 (incubation overnight, 4°C)

Wash and stabilisation of the plate (Saccharose, PBS, BSA, Na-azid; 2 h)

Adding of samples, standards and enzyme-labeled antigen incubation overnight, 4°C

Substrate (3,9 mmol/l o-Phenyldiamin; 5,4 mmol/l H₂O₂ in 0,066 mol/l citrate-phosphate-buffer, pH 5,0) (1 h)

Stopsolution (5 mol/l H₂SO₄)

Photometrically evaluation (492 nm)

Figure 2. Materials and methods.

RESULTS

In figure 3 and 4 we demonstrate the founded 6-Keto-PGF₁α and TXB₂-values from biopsies of superficial and solid basal cell carcinomas (n=62) in relation to clinically uneffected surrounding skin (controls).

In both histological types of BCC we found significantly higher 6-Keto-PGF₁α and TXB₂ contents in tumor tissue in comparison to control levels (p ≤ 0,05, u-test, Mann and Whitney). This means higher synthesis of PGI₂ and TXA₂ in tumor tissue.

In histological determined superficial basal cell carcinomas we could measure a 9 fold higher 6-Keto-PGF₁α and TXB₂ rates than in controls (uneffected skin). In solid BCC the relation of tumor tissue to controls of the two measured metabolites was 5 : 1 on average.

The TXB₂ content was two fold higher in solid BCC than in superficial BCC. In malignant melanomas we found clear increased levels (fig. 5) in the tumor surrounding tissue, also the same results we could state in squamous cell carcinomas (fig. 6).
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Figure 3. The synthesis of TXB$_2$ and 6-keto-PGF$_{1\alpha}$ in superficial BCC (A) and in surrounding skin (B)

Figure 4. The synthesis of TXB$_2$ and 6-Keto-PGF$_{1\alpha}$ in solid BCC (A) and in surrounding skin (B)
malignant melanomas

Figure 5. The synthesis of TXB$_2$ in malignant melanomas (A) and in surrounding skin (B)

squamous cell carcinomas

Figure 6. The synthesis of 6-Keto-PGF$_{1\alpha}$ in squamous cell carcinomas (A) and in surrounding skin (B)
DISCUSSION

Skin epidermis is a tissue exhibiting an active arachidonic acid metabolism (6). Effects on cutaneous microvascularization, chemotactic effects for leukocytes, fibroblasts and keratinocytes, growth promoting and immune regulatory effects are of particular interest with respect to the understanding of cutaneous physiology and pathophysiology (1, 11).

Vanderveen et al. (5) could show that there was a higher level of PGE$_2$ and PGF$_{2\alpha}$ in basal cell carcinomas than in normal epidermis. In our investigations we could also determined more arachidonic metabolites (PGF$_{1\alpha}$ and TXB$_2$) in BCC tissue than in clinically healthy skin. Higher levels of TXB$_2$ seem to be responsible for solid growth of BCC.

Several authors discussed an inverse relation of the metastatic potency of tumor types and the activity of arachidonic acid metabolism. Fitzpatrick et al. (10) and Schultz et al. (4) reported that tumors with high metastatic potency (melanomas and squamous cell carcinomas) had a lower arachidonic metabolite content than the surrounding skin. In tumors without metastatic activity relation was inverted (according our results). This tendency is possible explained by the antiaggregatorial effects of some prostanooids. It seems to be possible that cyclooxygenase and lipooxygenase products are involved in pathogenesis of tumor growth, differentiation and metastases. This could be indicating a criterion of malignancy for the prognosis of the tumor diseases.

CONCLUSION

Resulting from these examinations we see a relation between tumor growth, differentiation and formation of metastases.

A high metastatic frequency correlates with higher levels of the examined arachidonic metabolites in the tumor surrounding tissue than in tumor tissue.

Further investigations are obtained for differences in various regions of the patients body.

REFERENCES