



Studies on expression profiles in keratinocyte cancers with focus on basal cell carcinoma

av

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Abstract

Aims: This thesis aimed to investigate metabolic changes in keratinocyte carcinoma with a focus on basal cell carcinoma (BCC), to find potential treatment targets.

Material and Methods: Patients diagnosed with BCC (n=55) or cutaneous squamous cell carcinoma (cSCC, n=4) were included. Snap-frozen tumour tissue from BCC tumours, formalin-fixed paraffin-embedded tissue from BCC and cSCC tumours, and donor skin were investigated with quantitative real-time polymerase chain reaction (qPCR), microarray analysis, immunohistochemistry, and immunofluorescence. Cell lines from BCC, cSCC, and non-neoplastic keratinocytes were used to examine LAT1 inhibition with JPH203 in terms of decreased viability and changed gene expression in genes important for cell metabolism and carcinogenesis.

Results: SLC25A43 gene- and protein expression were significantly decreased in the BCC tumour samples (n=14) compared to the surrounding epidermis. Microarray examination of the tumour material (n=4+4) revealed increased expression of the amino acid transporters SLC7A5/LAT1 and SLC7A8/LAT2, which was confirmed with qPCR (n=14) and immunohistochemistry (n=14). The LAT1 expression was mainly in the centre of the tumours, and the fraction of LAT1-positive cells were significantly ($p<0.01$) inversely correlated to the proliferative active cells. Cleaved caspase 3 was significantly ($p=0.02$) increased in tumour areas with high LAT1 expression. In the patient cohort (n=57), the H-score for LAT1 was significantly higher ($p<0.001$) than for GLUT1 or GLI1. A sub-analysis of the BCC tumours also revealed a statistically significant correlation ($p<0.01$) between LAT1 and GLUT1 protein expression. The keratinocyte cell line (HEK001) showed significantly decreased viability when exposed to the LAT1 inhibitor JPH203 at concentration of 100 μM , and a low but significant upregulation of SLC7A5, SLC3A2, CCND1, ATF4 and GLI1 when exposed to a concentration of 10 μM JPH203.

Conclusions: Both SLC25A43 and LAT1 are altered in BCC tumours compared to normal skin suggesting metabolic changes in the tumours. The changed LAT1 expression might be explained by the harsh tumour environment. LAT1 could be a drug target for keratinocyte cancer, but needs further investigations in more advanced models.

Keywords: keratinocyte cancer, non-melanoma skin cancer, basal cell carcinoma, cutaneous squamous cell carcinoma, SLC25A43, LAT1