Cancer at high altitude

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1. Project description

Background Cancer mortality is reduced in human cancer patients living at high altitude (HA). The inverse relationship between HA and cancer mortality was first reported in human leukemia patients back in 1974. In the last decades these findings were confirmed after correcting for confounders such as industrialization, urbanization and ethnicity by several independent studies [1-4]. A recent study compared cancer mortality for Caucasians living at high and low elevated counties in the US [5] and showed a clear correlation between HA and reduced overall cancer mortality. Although overall cancer mortality negatively correlates with HA [2], cancer is a heterogeneous group of diseases that of course share many features but that also differ in etiology and pathology. Thus, site-specific cancer types may respond differently to HA: Indeed, HA exposure reduces mortality in lymphoma, breast [6], lung, tongue and mouth or larynx cancer [7, 8] but increases mortality in melanoma due to the higher background radiation at HA [9].

Next to human cancer patients, mice showed reduced tumor incidence at very high altitude (4540 m) after irradiating them with sub-lethal levels of x-rays [10, 11] as well as reduced incidence of spontaneous leukemia at HA [12]. This suggests that HA exposure may regulate common physiological and cell biological mechanisms that may reduce tumor onset and shift tumors towards a less malignant phenotype.

A lower malignancy at HA seems surprising because tumor tissue hypoxia per se promotes tumor growth and the development of aggressive phenotypes [13, 14]. Aggressive phenotypes develop even faster in combination with tumor-associated or therapy-induced anemia. However, in contrast to acute disease-associated anemia, humans living at HA prior to tumor onset are systemically adapted to hypoxia. HA-adapted highlanders reach a physiological and cell biological steady state that differs from the lowlander steady state. This difference might be the reason for reduced cancer mortality at HA and might hold a key to improve cancer treatment. However, the impact of chronic HA exposure on tumorigenesis is poorly studied: HA activates multiple adaptive mechanisms and thus, may impact on distinct cancer phases, namely, proliferation and metastasis (mortality), initiation (incidence) or cancer treatment (e.g. chemotherapy).

Results in 2018 – Taxol metabolism at HA We determined how high altitude exposure impacts on Taxol metabolism, distribution and chemotherapeutic resistance. We injected Lewis Lung Carcinoma cells, exposed tumor into C56Bl/6 mice and exposed these mice to high or low altitude exposure. After a single dose of 10 mg/kg Taxol, which was tail vein injected, we analyzed Taxol clearance from liver and tumor tissue via Liquid chromatography-mass spectrometry. Additionally, we analyzed the mRNA expression of genes (namely CYP2c38, CYP3a13, SLCO1b2 and PXR) involved in Taxol metabolism and genes (ABCB1a and ABCC10) involved in Taxol-resistance.

We observed that mice exposed to high altitude had a higher Taxol concentration in the tumor tissue but not in liver of mice exposed to low altitude (Fig.1). However, this finding was only observed 3 h after Taxol administration but not 6 or 8 h after Taxol injection. Although high altitude exposure per se changes the expression of Taxol metabolizing enzymes as well as transporters, no difference between Taxol treated mice at low and high altitude was observed. In addition, we also excluded differential gene expression of Taxol-resistance genes as the reason for improved Taxol efficacy at high altitude.

Our study supports previous findings that report a better tumor response to Taxol at high altitude. However, neither the liver Taxol metabolism nor Taxol resistance genes in the tumor seem to play a role in high altitude dependent Taxol efficiency suggesting that other physiological alteration, e.g. improved tumor angiogenesis, might cause a more efficient Taxol distribution in the tumor tissue.

Results in 2018 – Metastasis at HA Cancer malignancy and metastasis formation are the major reasons for cancer-related mortality. We investigated whether HA and the related hypoxia reduces metastasis formation. To study lung invasion as a crucial part of metastasis, we used C75BL/6 male mice and intravenously injected B16F10 melanoma cells. To quantify metastasis, we used histological methods (Hematoxylin and Eosin staining). In addition, we used real time PCR to estimate metastasis in the blood circulation and in the lymph system by analyzing the expression levels of Glycoprotein 100 (GP100) and tyrosinase-related protein 2 (TRP-2) – two specific melanoma markers. Our results show that B16F10 melanoma cells invaded the lung after i.v. injection but no difference between LA and HA exposed mice was observed.

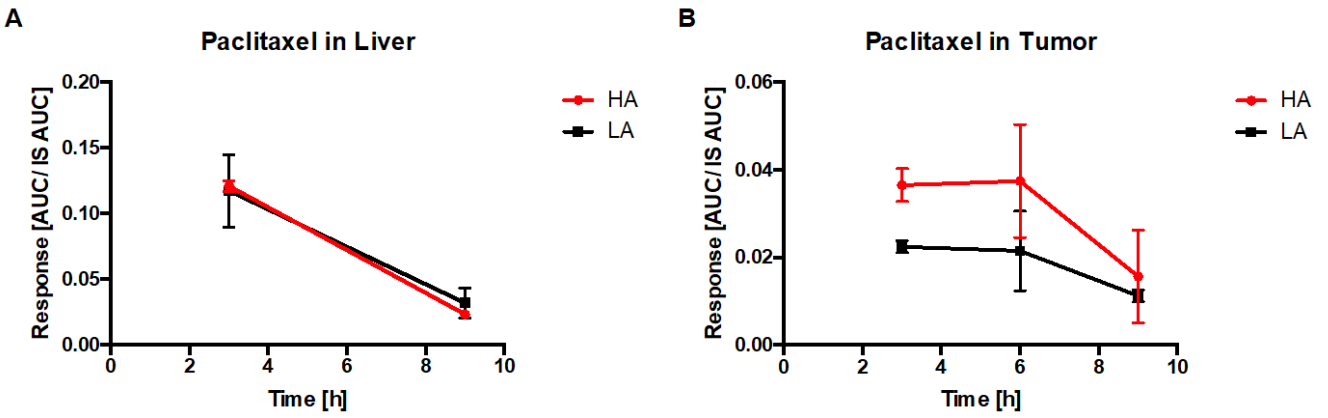

Figure 1. Liver and tumor relative concentration-time profiles of Paclitaxel in LLC1 tumor bearing C57Bl/6 mice after a single intravenous administration dose of 10 mg/kg Taxol. Shown is the area under the curve (AUC) normalized to internal standard AUC (y-axis) blotted against the time (x-axis) for liver (A) and tumor (B) from mice exposed to low (LA, black) or high altitude (HA, red). Shown is the mean and standard deviation and a 2-way ANOVA test with a Bonferroni post-test was performed (n=3) (unpublished data, taken from Master thesis Minh Tri Le).

However, mice exposed to HA showed a lower gene expression of GP100 and TRP-2 than LA exposed mice (Fig. 2), suggesting that the invasion of the lymph system might be reduced at HA.

In conclusion, our data show that HA exposure does not alter the invasion of cancer cells into tissues but may rather inhibit the invasion of the lymph system, which is the predominant route of cancer cell migration and a critical step in the metastasis process.

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Internet data bases

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Scientific publications and public outreach 2018

Refereed journal articles and their internet access

Thiersch, M. and E.R. Swenson, Cancer at high altitude, High Altitude Medicine & Biology, **19**, 2, 2018. https://doi.org/10.1089/ham.2017.0061

Conference Papers

ThiThiersch, M., N. Jaenicke, J. Armburster, T. Haider, N. Fabregas Bregolat, N. Kachappilly, E.S. Gasser, M. Gassmann, High Altitude and Cancer, 9th Atacama-Leh conference on coping with hypoxia at high altitude: How lung, blood and brain respond and crosstalk, San Pedro de Atacama, Chile, March 4-9, 2018.

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Theses

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Cosi, G., The impact of high altitude as well as hypoxia exposure on metastasis formation and spreading, Master Thesis, University Zurich, Start 2018, End January 31st 2019.

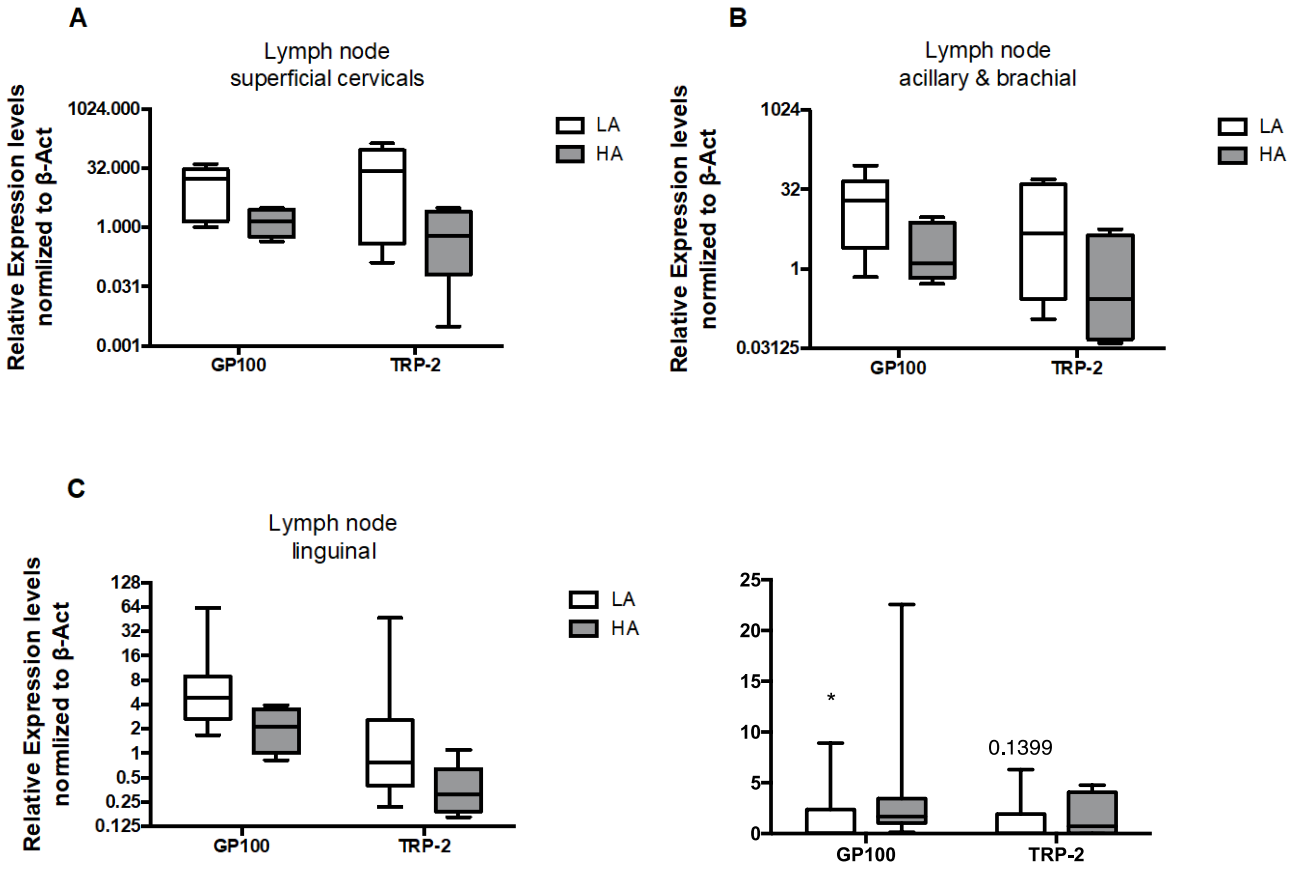

*Figure 2. RT-qPCR data of two melanoma markers in three different lymph nodes and blood cells of B16F10 injected C57Bl/6 mice exposed to low or high altitude. Glycoprotein 100 (GP100) and Tyrosine-related protein 2 (TRP-2) mRNA expression levels of (A) superficial cervical, (B) axillary and brachial and (C) inguinal lymph nodes as well as (D) blood cells were quantified by real time PCR and normalized to mRNA β-actin levels to obtain relative expression levels. Shown are box plots of samples from low (white) and high altitude (grey) exposed mice with whiskers representing min to max. Y-axis of panel A to C are log2. Mann-Whitney test was performed, *p≤0.05. (unpublished data, taken from Master thesis Glenda Cosi).*

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