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P01.16 EFFECTS OF THE STAT3 INHIBITORS ON SENESCENT TUMOUR CELLS

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Background Cellular senescence is the process of cell proliferation arrest. Premature cellular senescence can be induced by chemotherapy, irradiation and, under certain circumstances, by cytokines. Senescent cells produce a number of secreted proteins and growth factors that may either stimulate or inhibit cell proliferation. One of the major cytokines that play role in regulation of cellular senescence is IL-6. IL-6/STAT3 signaling pathway represent decisive regulatory factors in cellular senescence. The objective of this study was to compare the effects of the STAT3 inhibitors on senescent and proliferative tumour cells. Further, the therapeutic potential of the STAT3 inhibitors was evaluated using murine tumour models.

Materials and Methods *In vitro*, as well as *in vivo* experiments were performed using TC-1 (model for HPV16-associated tumours) TRAMP-C2 (prostate cancer) cell lines. C57Bl/6NCrl mice, 7–8 weeks old, were obtained from Velaz (Prague, Czech Republic). Experimental protocols were approved by the Institutional Animal Care Committee of the Institute of Molecular Genetics (Prague, Czech Republic). STAT3 inhibitors, namely STATTIC, BP-102 (synthesised at the University of Hradec Kralove) and their derivatives were tested for their effects on tumour cells, such as cytotoxicity, ability to inhibit STAT3 phosphorylation, cell proliferation and tumour growth in syngeneic mice.

Results We have previously demonstrated that docetaxel-induced senescence in the TC-1 and TRAMP-C2 murine tumour cell lines, which was proved by *in vitro* (detection of increased p21 expression, positive beta-galactosidase staining, and the typical SASP capable to induce 'bystander' senescence), and *in vivo* experiments, using C57BL/6 mice [1]. Both TC-1 and TRAMP-C2 cells displayed elevated IL-6 secretion and activated STAT3 signaling pathway. Therefore, we tested efficacy of the STAT3 inhibitors on these cell lines. Cytotoxic and STAT3 phosphorylation inhibitory effects of the inhibitors were observed in both proliferating and senescent cells. Antitumor effects of selected inhibitors were evaluated.

Conclusions Collectively, STAT3 is an attractive target for therapeutic approaches in cancer treatment and we can assume that inhibition of the STAT3 pathway can be used for elimination of the pernicious effects of the senescent cells.

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P01.17 TIM-3/GALECTIN-9 PATHWAY CONTROLS THE ABILITY OF MALIGNANT CELLS TO ESCAPE HOST IMMUNE SURVEILLANCE. REGULATORY MECHANISMS AND THERAPEUTIC TARGETS

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Background Human cancer cells implement a variety of biochemical mechanisms which allow them to escape host immune surveillance resulting in disease progression. We have reported that the immune receptor Tim-3 and its natural ligand and possible trafficker galectin-9 determine the capability of human acute myeloid leukemia (AML) cells to evade cytotoxic immune attack.[1] Our further studies demonstrated that breast, colorectal and other human solid malignant tumour cells display high activity of this pathway[2] which can also be used for immune evasion. It is, however, important to understand the mechanisms which regulate the biochemical activity of Tim-3/galectin-9 pathway and expression of its components as well as the molecular basis of its capability to impair anti-cancer activity of cytotoxic lymphoid cells.

Materials and Methods In this study we used human cancer and non-malignant cell lines as well as primary human malignant tumour samples. We also used primary human T cells and natural killer (NK) cells. Western blot analysis, ELISA, quantitative real-time PCR, on-cell Western, immunohistochemistry, flow cytometry and biochemical assays were used as key instrumentals to conduct measurements.

Results We found that galectin-9 is used by human cancer cells to escape host immune surveillance. Cancer cells use various biochemical pathways to overexpress galectin-9. Regardless the biochemical background, transforming growth factor-beta (TGF-β) and transcription factor Smad-3 play crucial role in galectin-9 expression in human cancer cells. We identified the key receptors through which galectin-9 can then trigger killing of cytotoxic T lymphocytes and impairing of anti-cancer activity of natural killer cells.

Conclusions In this work, we report the biochemical mechanisms underlying overexpression of galectin-9 in human

malignant tumour cells and its differential effects on human cytotoxic lymphoid cells.

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P01.18 METABOLIC STATUS AND IMMUNE ACTIVATION INFLUENCE CLINICAL OUTCOMES IN PATIENTS AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

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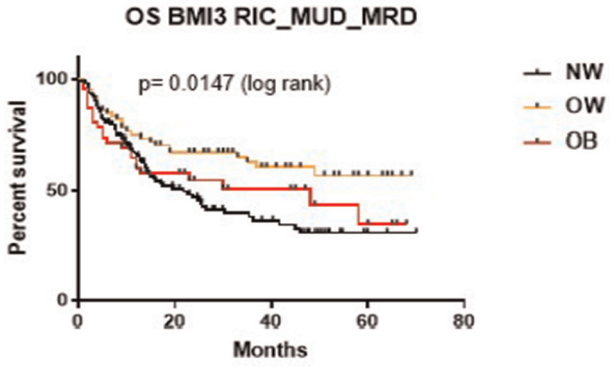
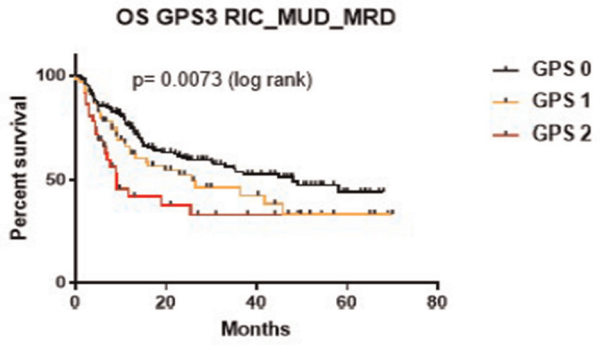
Background The nutritional status is an important factor contributing to non-relapse mortality for patients undergoing allogeneic hematopoietic stem cell transplantation (alloHSCT). In contrast to underweight, the role of overweight and obesity for alloHSCT outcomes is less well understood. This might be due to the use of the body-mass-index (BMI) as a classic measure of metabolic risk, which does not necessarily reflect body composition and visceral obesity. Importantly increased inflammation and malnutrition (Glasgow-Prognosis-Score, GPS) as well as increased neutrophil-to-lymphocyte ratios (NLR) have been described as adverse prognostic factors for a variety of solid tumors. In alloHSCT the GPS and NLR are ill defined so far. Here, we analyzed the impact of pretransplant GPS and d+100 NLR in correlation to the BMI on clinical outcomes following alloHSCT.

Materials and Methods Clinical data of consecutively treated patients between 2012 and 2017 at our transplant center were analyzed. From these cases only matched (10/10) related and unrelated donors and reduced intensity conditionings were included into the analysis. Based on BMI and GPS prior to conditioning we defined three groups respectively: normal weight (NW), overweight (OW), obese (OB); and GPS 0 (CRP<10 mg/dl, normal protein), GPS 1 (CRP >10 mg/dl, normal protein), GPS 2 (CRP >10 mg/dl, low protein). NLR at d+100 were also analyzed. We focused on survival and mortality until the data lock. Incidence rates of acute graft-versus-host disease (aGvHD) were determined until day+100.



Abstract P01.18 Figure 1



Abstract P01.18 Figure 2

Results From a total of 464 identified records, 265 cases were included into the analysis based on the inclusion criteria. Median overall survival in OB patients was doubled compared to NW (48 vs. 21.8 months; p=0.01) and in OW patients median overall survival was not reached (figure 1, *not included in the submitted abstract)*. Pretransplant GPS could also dissect survival curves with worst OS for patients with GPS 2: 9 (GPS 2) vs. 25.6 (GPS 1) vs. 48 (GPS 0) months, p=0.007). However, GPS values did not correlate with BMI (figure 2, *not included in the submitted abstract)*.

Increased d+100 NLR correlated non-significantly with poorer survival and increased relapse rates. There was a trend to increased clinically relevant aGvHD (≥II°) in GPS 2 individuals, not detectable according to BMI groupings.

Conclusions There is a need for better immunometabolic risk measures in patients before alloHSCT. Our data suggest that pretransplant GPS and NLR could be of value for risk estimations and further validation is warranted.

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P01.19 ABSTRACT WITHDRAWN

P01.20 TIM-3-GALECTIN-9 IMMUNOSUPPRESSIVE PATHWAY IN HUMAN LIQUID AND SOLID TUMOURS

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Background In recent years there has been increasing evidence highlighting biochemical pathways operated by human cancer cells, which allow them to escape host immune surveillance. Understanding the molecular basis of these immune evasion pathways and mechanisms underlying their biochemical regulation would allow development of fundamentally novel strategies of anti-cancer immunotherapy. This work is devoted to understanding the pathological role of Tim-3-galectin-9 immunosuppressive pathway.