Immunotherapy has become an essential component of cancer treatment, however, a majority of patients with solid metastatic cancers, such as pheochromocytoma (PHEO), do not respond to this type of therapy. Recently, we developed an intratumoral (i.t.) immunotherapy based on the unique combination of TLR ligands, anti-CD40 antibodies, and mannan, which is artificially bound to tumor cells via an anchor (MBTA therapy). This therapy resulted in the complete eradication of aggressive subcutaneous PHEO in 67% of mice and demonstrated a systemic antitumor immune response and regression of non-treated lesions in the metastatic model (1). To further evaluate this systemic effect generated during MBTA therapy, we established a murine bilateral PHEO model, where MBTA therapy was i.t. injected into one tumor, and the distant (non-treated) tumor was monitored for changes in size and immune cell infiltration. The growth of both MBTA-treated and distant tumors was reduced compared to that of the control. Interestingly, survival of the MBTA-treated mice was twice as long compared to the control mice. Moreover, we have made several unique observations during the experiments which were focused on the tumor microenvironment. Flow cytometry analysis revealed the ability of MBTA therapy to significantly increase the infiltration of innate immune cells (monocytes, DCs, macrophages, NK cells) not only in MBTA-treated tumors, but also in distal tumors, despite the fact that MBTA therapy was designed to elicit only local inflammation. An analysis of the macrophage phenotype revealed a switch from protumor M2 to antitumor M1 macrophages in both tumors during the entire MBTA therapy treatment. Analysis of splenic adaptive immune cells revealed that naïve CD4+ or CD8+ T cells differentiated into central memory cells and effector memory cells. CD4+ and CD8+ T cells were elevated in MBTA-treated and distant tumors with a significantly higher frequency of CD8+ effector memory T cells. Moreover, the adoptive transfer of CD4+ and CD8+ T cells revealed that immune memory, after tumor rechallenging, was driven by CD4+ T cells. Collectively, these results illustrate the ability of MBTA therapy to activate both parts of the immune system and render a systemic antitumor response against non-treated metastases. We believe that our results could lead to the use of MBTA therapy in patients with aggressive, metastatic lesions. **Reference:** Caisova et al., Cancers (Basel), 2019. 11(5).

Tumor Biology

HORMONE ACTIONS IN TUMOR BIOLOGY: FROM NEW MECHANISMS TO THERAPY

Taking Advantage of the TGFB1 Biology in Differentiated Thyroid Cancer to Stimulate Sodium Iodide Symporter (NIS)-Mediated Iodide Uptake in Engineered Mesenchymal Stem Cells

Yang Han, MD student, Viktoria F. Koehler, MD, Nathalie Schwenk, Technician, Kathrin A. Schmohl, PhD, Rebekka Spellerberg, PhD student, Carolin Kitzberger, PhD student, Peter J. Nelson, PhD, Christine Spitzweg, MD.
University Hospital of Munich, LMU Munich, Munich, Germany.

The sodium iodide symporter (NIS) mediates the active transport of iodide into thyroid follicular cells, providing the basis for the use of radioiodide for diagnostic imaging and therapy of differentiated thyroid cancer and also non-thyroidal tumors after tumor-selective *NIS* gene transfer. Based on their excellent tumor-homing capacity, mesenchymal stem cells (MSCs) can be employed as tumor-selective *NIS* gene delivery vehicles. Transgenic expression of *NIS* in genetically engineered MSCs allows noninvasive imaging of functional *NIS* expression as well as therapeutic application of ^{131}I. The use of promoters activated by tumor micromilieu-derived signals to drive *NIS* expression enhances selectivity and effectiveness, while limiting potential off-target effects. In this study we aimed to exploit the central role of transforming growth factor B1 (TGFB1) in tumor milieu-associated signaling using a TGFB1-inducible synthetic SMAD-responsive promoter to selectively drive *NIS*-transgene expression in engineered MSCs (SMAD-NIS-MSC) in the context of differentiated thyroid cancer based on the critical role of TGFB1 in the pathogenesis of radioiodine refractory differentiated thyroid cancer. To evaluate the TGFB1 expression in thyroid cancer cell lines, the TGFB1 concentration in conditioned medium (CM) from an array of established human papillary thyroid cancer (PTC) cell lines (BCPAP and K1) was measured by ELISA. BCPAP-CM showed a higher concentration of TGFB1, while a lower concentration was measured in K1-CM. Stimulation of SMAD-NIS-MSCs with PTC-CM showed a significant increase of NIS-mediated radioiodide-125 uptake in these MSCs *in vitro*. In addition, iodide uptake in SMAD-NIS-MSCs was significantly stimulated by co-culture with thyroid cancer cells. Cell migration assay was performed to validate the effect of PTC-CM in MSC recruitment. MSCs subjected to a gradient between tumor CM and serum free medium showed a directed chemotaxis towards CM with increased forward migration index (FMI) and center of mass (CoM). In a next step, based on the *in vitro* studies, SMAD-NIS-MSCs will be systemically applied via the tail vein to mice harboring subcutaneous PTC tumors and tumoral iodide uptake will be monitored by ^{123}I-scintigraphy. Taken together, these data indicate the feasibility of commandeering TGF-β/SMAD signaling in the TGFB1-rich tumor environments of radioiodine refractory differentiated thyroid carcinomas to re-establish functional *NIS* expression using engineered mesenchymal stem cells as therapy vehicles.

Tumor Biology

HORMONE ACTIONS IN TUMOR BIOLOGY: FROM NEW MECHANISMS TO THERAPY

Targeting Glycogen Metabolism as a Novel Therapeutic Approach in Anaplastic Thyroid Cancer

Cole Davidson, BS, Jennifer Tomczak, MPH, Eyal Amiel, PhD, Frances Carr, PhD.
University of Vermont, Burlington, VT, USA.

Effective treatment options for well-differentiated papillary (PTC) and follicular (FTC) thyroid cancers afford positive patient prognoses. The absence of effective interventions for the stem-like, dedifferentiated anaplastic thyroid cancer (ATC) results in poor patient outcomes with a mortality rate higher than all other endocrine cancers combined (1). While receptor tyrosine kinase inhibitors such as sorafenib