St. Anna Kinderkrebsforschung
CHILDREN'S CANCER RESEARCH INSTITUTE

MiRNAs & DC THERAPY

MicroRNA profiling of tumour tissue as a predictive marker for the clinical outcome of patients treated with a novel Dendritic Cell-based active immunotherapy

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Abstract

My current research at the Children's Cancer Research Institute (CCRI) is centered around the role of cells found in excised tumour tissue for cancer immunotherapies based on Dendritic Cells. In this project, the focus is on microRNAs that influence the biology of e.g. cancer stem-like cells and immune cells.

Scientific Rationale:

Medicine has made great progress in the prevention and early detection of malignancies in recent years, but cancer is still the second most common cause of death in developed countries. To overcome these therapeutic shortcomings, a number of experimental treatments are currently evaluated in clinical studies. Among them is the active cellular immunotherapy with Dendritic Cells (DCs) developed by the Tumour Immunology Laboratory of St. Anna Children's Cancer Research Institute (CCRI). Although this novel therapy could potentially be used against a multitude of malignancies, it is now as a first step tested against glioblastoma multiforme. The treatment process involves yielding a patient's own monocytes via leukocyte apheresis, differentiating them into DCs and loading them with the same patient's tumour tissue lysate that was obtained during a first-line surgical therapy. The DCs process and present the tumour antigens in an MHC context on their surface. With the help of a microbial danger signal (lipopolysaccharide, LPS) and interferon gamma (IFNγ) the DCs are then activated and injected into the patient's lymph nodes in parallel to the standard treatment with chemotherapy and radiation. This way, the DCs are supposed to trigger an anti-tumour immune response. Pre-clinical and phase I clinical data so far show the safety and feasibility of the approach, while statistical efficacy is currently explored in a multi-center phase II clinical trial involving nearly all major hospitals in Austria.

Tumours show a heterogeneity of cell types, among them bulk cancer cells, cancer stem-like cells and immune cells. The interplay of these cell types already *before* the start of an immunotherapy will potentially influence the outcome of such a treatment approach. Of special interest across all species of tumour cells is the role of miRNAs. As regulators of gene expression levels, they have been shown to strongly influence cancer development, states of "stemness" and immune reactions. Hence, it is scientifically sound and interesting to focus on the role they play for our novel DC-based immunotherapy and whether they could be used as predictive biomarkers.

Objectives:

This project aims at identifying miRNA profiles of tumour tissue as potential biomarkers to predict the efficacy of the DC-based immunotherapy described here. Samples from patient tumours will be analyzed via miRNA profiles of the excised tissue containing e.g. bulk tumour cells, cancer stem-like cells and immune cells. This information will then be correlated with survival data and other clinical endpoints. The connection of miRNA profiles and patient data shall then lead to the establishment of predictive biomarkers.

Methods:

Since the production process of the vaccine, as outlined above, involves excised tumour tissue, single cell suspensions of all participating patients are stored for quality control reasons. All samples from

patients that have been treated with the CCRI DC active immunotherapy in the course of clinical studies are therefore in principle available for analysis. By entering into the studies, the patients have already given informed consent that their tissues will be studied.

Handling of the samples as well as preparatory work for the miRNA profiling means using classic cell biology techniques. For the actual measurement of the miRNA profiles, commercially available miRNA array kits will be used that cover all miRNAs with a published connection to immunology, “stemness” and cancer.

Originality and Relevance:

The successful treatment of malignant diseases is, despite all efforts, a medical need that is still unmet. Active immunotherapies with e.g. dendritic cells could be a future treatment modality. Given the novelty of this approach, biomarkers to identify patients with a promising treatment response have yet to be identified. The work described here is a first effort to establish such biomarkers for the DC-based approach followed by St. Anna Children’s Cancer Research Institute, focusing on miRNAs with a role in immunology, “stemness” and cancer.

Prospect:

If a correlation between specific miRNA profiles and specific clinical endpoints can be established, this will enhance our understanding of the molecular mechanisms at the interplay of cancer bulk cells, cancer stem-like cells and immune cells. Furthermore, knowledge gained within this project shall lead to the development of predictive biomarkers, which is relevant for further studies as well as the possible future standard clinical application of any DC cancer vaccine.