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UMESciA project Jendrossek Laboratory
(in collaboration with Dept. of Radiotherapy, Prof. Dr. Martin Stuschke)

Relevance of biological factors to outcome of radio(chemo)therapy or radio(chemo)therapy-immunotherapy combinations in advanced solid human tumors

Background:

Concurrent radiochemotherapy (RCTx) and immune checkpoint inhibitor (ICI) therapy have increased survival rates in advanced non-small cell lung cancer (NSCLC) and advanced squamous cell carcinoma of the head and the neck (HNSCC) (1, 2). Besides their well-known direct cytotoxic action, radiotherapy (RT) and cytotoxic chemotherapy (CTx) reprogram the tumor microenvironment (TME), and augment local and systemic antitumor immune responses under certain conditions, particularly when combined with immunotherapy (IT). Innovative treatment concepts therefore combine ICI therapy with standard radiotherapy (RT) or RCTx in order to achieve synergistic antitumor responses (3) and improve therapy outcome, e.g., in patients with advanced NSCLC (4, 5). Promising results of PD1/PD-L1 based ICI therapy in recurrent or metastatic HNSCC (6-8) have also stimulated the clinical development of ICI in combination with RCTx in the curative setting.

Despite improved multimodal therapy, there is still a high risk of therapy failure by locoregional recurrence or metastasis so that prognosis of patients with advanced solid tumors remains poor. The rationale for combining RT or RCTx with ICI therapy is based on the reciprocal induction of common immune effector mechanisms that are linked to efficacy (9-11), whereas tumor-induced or therapy-induced increase in immuno-suppressive cells or mediators may be causative for the limited success of ICI therapy (12). These variables will also impact the risk of developing therapy-induced immune-related adverse effects (irAE), e.g., in the lung and the heart, upon single or combined treatment (13-15).

So far, reliable biomarkers predicting likelihood of RCTx response or risk of recurrence or adverse effects in individual patients are mostly missing. Emerging biomarkers beyond molecular subtype for NSCLC patients or Human Papilloma Virus (HPV)-status (for oropharyngeal squamous cell carcinoma (16)), several aspects of the immune phenotype (17-19) had prognostic value in HPV-negative HNSCC patient cohorts receiving postoperative RCTx, and may also increase the likelihood for response to ICI therapy (2).

Previous work

Our interest focuses on the contribution of tumor-induced, environment-induced and therapy-induced immune mechanisms to therapy failure (primary vs. secondary resistance) or adverse effects of RT or RCTx without or with additional IT in patients suffering from solid human tumors. We have broad experience in preclinical investigations aimed at a biological optimization of RT including the definition of prognostic biomarkers and the identification of therapeutic targets in HNSCC and NSCLC (20-25). Our previous work indicates that RT-induced senescence and reprogramming of the lung environment contribute to facilitated seeding and growth of circulating tumor cells in previously irradiated lung tissue as well as RT-induced pulmonary fibrosis; targeted inhibition of pathology-associated changes in the host immune environment attenuated RT-induced these unfavorable effects in murine models ((26-31)). RT-induced changes in environmental factors altered recruitment and pathologic differentiation of cells from the myeloid compartment and their regulatory cross-talk with cells from the adaptive immune system, particularly T cells, with impact on efficacy and toxicity of RT/RCTx and ICI therapy, and their combination suggested by others (32) and own unpublished work.

Aims and work Program:

There is high medical need to define prognostic markers indicating probability of response and increased risk of recurrence RT, RCTx and IT, and to design more effective combinatorial treatments that reduce the risk of local or distant failure upon and improve therapy outcome in advanced HNSCC (and NSCLC). The proposed project aims to explore how the tumor-induced and therapy-induced changes in the composition of immune cells and cytokines in the peripheral blood and in the TME impact recruitment, phenotype and function of T cells and myeloid cells and the outcome of RT/RCTx and ICI therapy.

Specific aims are as follows:

i) We will use biomaterial from ongoing studies and already collected conserved or vital samples from our co-clinical **murine** HNSCC and NSCLC models to systematically profile composition and phenotype of cells from the innate and adaptive immune system and of immune mediators before therapy and also record time-dependent changes in the host immune repertoire upon exposure to RT, ICI. or the combination (blood/plasma samples; circulating immune cells; tissue samples). We assume that the detailed evaluation of the host immune environment before and under therapy will provide new mechanistic explanations for response or resistance to RT/RCTx, and RT/RCTx-IT combinations and associated immune escape or adverse effects. These findings will reveal additional molecular or immunological determinants that could be used for the design of rational therapeutic strategies suited to avoid primary resistance, relapse, or adverse effects and thereby to optimize therapies involving RT without or with IT in the future. Assumed immune mechanisms underlying therapy failure may be validated in our preclinical models.

ii) We will use biomaterial and molecular data available from ongoing studies and already collected conserved or vital samples (blood/plasma samples/circulating immune cells) from studies with HNSCC (or NSCLC patients) before, during, or after RCTx, ICI therapy, or the combination, if they can be obtained in collaboration with our clinical partners from the Dept. of Radiation Therapy, the Dept. of Otorhinolaryngology and Head and Neck Surgery, and the Dept. of Pathology, to systematically profile various aspects of the host immune environment.

iii) We will use data obtained in aim 1 and 2 as well as datasets from publicly available studies to associate tumor-specific and therapy-induced host immune repertoires with data on tumor response and therapy outcome. Correlation of the data obtained in aim 1 and aim 2 with outcome data upon RT/RCTx and ICI therapy shall provide a scientific basis to define candidate molecular markers or marker patterns suited to predict likelihood of response or risk of therapy failure or adverse effects upon RT/RCTx without or with ICI therapy for future patient stratification (for bioinformatic analyses: collaboration with Prof. Dr. M. Stuschke, Prof. D. Hoffmann; Dr. F. Farahpour). Promising candidate biomarker identified by these investigations will be validated in patient samples (cooperation with Prof. M. Stuschke; Prof. S. Brandau; Prof. S. Lang).

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