Project proposal for a Joint Tandem Research Project within the DKFZ-Princess Margaret Cancer Center Clinician and Medical Scientist Program

Project Title

The role of tryptophan catabolism in the regulation of anti-tumor immunity

Key Words

Tryptophan catabolism, tumor microenvironment, anti-tumor immunity, immunotherapy

Information on hosting groups

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Summary of the Tandem Research Project

The role of tryptophan catabolism in the regulation of anti-tumor immunity

Rationale:

The intricate interplay between the immune system and cancer cells has been a focal point in cancer research, with recent advancements highlighting the pivotal role of immune checkpoints in modulating anti-tumor responses. Tryptophan, an essential amino acid, has emerged as a key player in this context due to its involvement in the indoleamine 2,3-dioxygenase 1 (IDO1), tryptophan 2,3-dioxygenase (TDO1) and interleukin-4-induced 1 (IL4I1) pathways, all of which lead to the catabolism of tryptophan. In addition, also the microbiome, which has recently emerged as an important regulator of anti-tumor immunity catabolizes tryptophan to indole metabolites.

Tryptophan catabolism generates immunosuppressive metabolites, creating a permissive environment for tumor growth and immune evasion. However, the specific mechanisms governing the interplay between tryptophan catabolism and the immune system remain unclear. By unraveling these intricacies, our proposed research aims to uncover novel insights into the immune checkpoint landscape, providing a more comprehensive understanding of the factors influencing tumor-immune interactions.

This research proposal aims to elucidate the intricate mechanisms through which tryptophan catabolism influences the regulation of anti-tumor immunity. Specifically, we will investigate the impact of tryptophan metabolites on immune cell function, tumor microenvironment modulation, and the overall anti-tumor response. The proposed study will employ a multidisciplinary approach, combining immunological, molecular, and biochemical techniques to comprehensively address the following key objectives:

1. Characterize tryptophan catabolism in the tumor microenvironment: Employ high-throughput sequencing and mass spectrometry techniques to profile the expression levels of key enzymes and metabolites involved in tryptophan catabolism within the tumor microenvironment.
2. Evaluate the influence of tryptophan metabolites on immune cell function: Utilize in vitro co-culture systems of immune cells and tumor cells to investigate the effects of tryptophan catabolites on immune cell activation, differentiation, and effector functions.
3. Assess the impact of tryptophan catabolism on tumor immune evasion: Utilize murine tumor models to study the influence of tryptophan catabolism on tumor growth, metastasis, and evasion of immune surveillance. Implement gene editing techniques to modulate tryptophan catabolism in vivo.

Impact towards patient-related translational cancer research:

The proposed research has the potential to significantly impact translational cancer research by advancing our understanding of tryptophan catabolism in the context of anti-tumor immunity. The translational implications include the development of predictive biomarkers, targeted therapies, and improved treatment strategies, ultimately fostering a patient-centered approach in the fight against cancer.

Exchange between the McGaha and Opitz laboratories:

Both laboratories have a strong track record in tryptophan catabolism in cancer. The McGaha laboratory will provide expertise in microbiome research, murine models and immunology. The Opitz laboratory will contribute medical expertise and metabolomics.