ImmunoTools *special* Award 2025

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Exploring GDF15 as a Key Modulator of Tumor Immune Microenvironment and Therapy Resistance in Esophageal Adenocarcinoma

Background

According to a new global report[1], Esophageal cancer (EC) is the ninth most common malignant tumor and the sixth most common cause of cancer-related deaths. The two main pathological subtypes of EC are esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). In recent years, the development of immunotherapy including adoptive cell transfer and immune checkpoint inhibitors (ICIs) has revolutionized cancer treatment[2–4] . ICIs targeting programmed death receptor 1 (PD-1) and its ligand (PD-L1) have been proved to be promising in the treatment of kinds of cancers, also in esophageal cancer. However, only 20-40% of patients will benefit from ICIs and even fewer will have long-term disease control[5,6]. Cancer comprises malignant cells surrounded by the tumor microenvironment (TME), a dynamic ecosystem composed of tumor cells and several non-tumoral components such as stromal cells, including fibroblasts (often referred to as cancer-associated fibroblasts [CAFs]); endothelial cells; immune cells, like neutrophils, macrophages, and lymphocytes; and the non-cellular components of the extracellular matrix (ECM) such as collagen, fibronectin, hyaluronan, laminin, among others[7]. A key pathway through which tumors evade the immune system is the reprogramming of cellular constituents of the TME towards an immunosuppressive phenotype. Thus, enhancing the effectiveness of immunotherapies by manipulating the TME is a major focus of current research.

Growth differentiation factor 15 (GDF15), originally described as macrophage inhibitory cytokine-1, is a distant member of the transforming growth factor-β superfamily and is considered a stress responsive cytokine induced by mitochondrial

dysfunction, cellular stress, inflammation or mitochondrial unfolded protein response (UPRmt) pathway, with positive effects on health and lifespan of model organisms[8]. GDF15 expression is very low in healthy individuals and young subjects, the levels of GDF15 dramatically increase in chronic or acute illness conditions, in presence of age-related diseases, such as cancer, cardiovascular diseases, insulin resistance and type 2 diabetes, as well as neurodegeneration[9-10]. In a large-scale screening, GDF-15 was the most prominently overexpressed soluble factor across a large range of cancer types[11]. In esophageal cancer, elevated GDF-15 was positively associated with tumor invasion, lymph node metastasis, and shorter relapse-free and tumor-specific survival. Moreover, GDF-15 was the strongest predictor for outcome compared with other markers tested in the same patient cohort[12]. The potential mechanisms by which GDF15 facilitates tumor immune evasion include the reduction of infiltrating T cells, suppression of dendritic cell maturation, and induction of a tolerogenic/immunosuppressive phenotype in macrophages[13].

The previous work conducted by our research group has successfully established the cultivation of primary cells from EAC tissues and the development of human 3D organoid models. It has been demonstrated that CAFs secrete GDF15, which promotes the growth of EAC. This study will further investigate the role of GDF15 in EAC from the aspects of tolerogenic/immunosuppressive TME: As a cytokine, which immune cell subsets in the tumor microenvironment are mainly affected by GDF15? What are the main pathways through which GDF15 affects them (metabolism, apoptosis, and others?)? Can immune tolerance be reversed by intervening in GDF15?

Experimental Design & Methods

A preliminary in vitro study phase is expected where we will resemble what we would perform with the FACS technology in EAC.

I. PBMC (Peripheral Blood Mononuclear Cells) and PMN (Polymorphonuclear Neutrophils) from healthy donors (n=5) and EAC patients (n=5) will be separated and cultured. Then, PBMC and PMN will be treated with rhGDF15 for 20mg/L, 12-24 hours(PBMC), or 3-6 hours (PMN). Flow cytometry will be used to identify changes in the number and phenotype of immune cells following rhGDF15 treatment compared to the control.

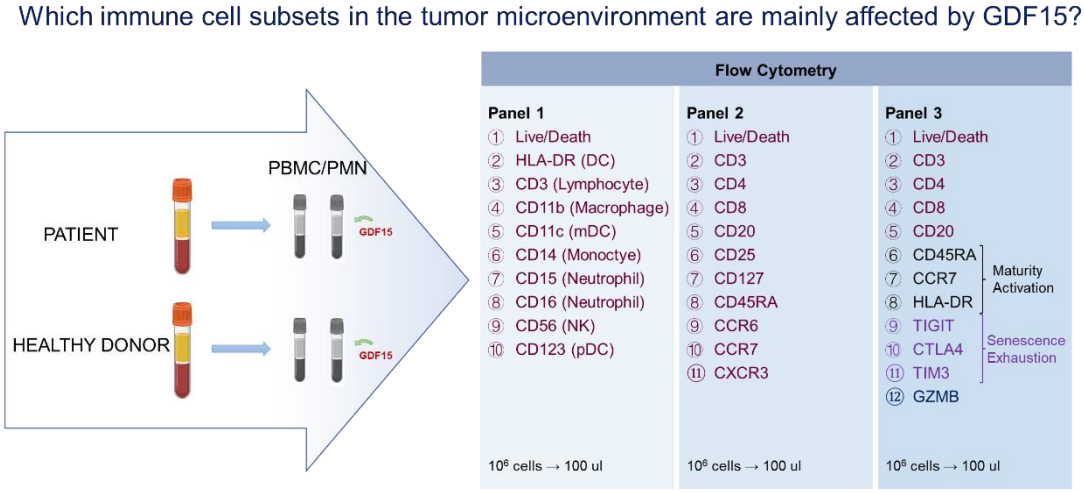
II. Screen 1–2 of the most impactful cell types for subsequent in-depth studies. For example, in an EAC tumor-bearing mouse model, selectively knock out GDF15 in specific cells and administer PD-1 antagonists to compare changes in tumor growth and invasion, as well as variations in infiltrating immune cell subpopulations and functions. Alternatively, in the EAC tumor-bearing mouse model, compare the therapeutic effects of GDF15 antagonists combined with PD-1 antagonists versus PD-1 antagonists alone.

Impact

Our project aims to investigate the mechanisms of immunotherapy resistance in EAC and identify potential intervention targets, thereby offering the possibility of clinical benefits for patients.

Cooperation partner

The group of PD Dr. Yue Zhao and Prof Dr Hans Schlösser (Cologne Translational Immunology) will work together to support Mr ZiCheng Lyu to adjust the experimental and instrumental set-up to conduct analysis for PBMC and PMN.



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