Novel immunotherapy targets: the druggable immune GPCRome and new immune-evasive cancer drivers

J. Silvio Gutkind

Department of Pharmacology, School of Medicine, and Mores Cancer Center, University of California San Diego (UCSD)

Abstract

Immune checkpoint blockade (ICB) targeting PD-1 and CTLA-4 has revolutionized cancer treatment. However, many cancers do not respond to ICB, prompting the search for additional strategies to achieve durable cancer remission. In this regard, G-protein-coupled receptors (GPCRs) represent the largest family of cell surface receptors involved in signal transduction and are the target of >30% of all FDA-approved drugs. GPCRs are the most pharmacologically favorable drug targets, but they have been largely underexploited in oncology and cancer immunotherapy. Recently, we cross-integrated large single-cell RNA-sequencing (scRNAseq) datasets from CD8+ T cells and identified an enrichment of Gαs-coupled GPCRs on exhausted CD8 T cells. Further studies revealed that tumor cells may avoid CD8 T cell recruitment and immune elimination by stimulating Gαs-GPCRs on infiltrating CD8 T cells, thereby representing druggable immune checkpoints that can be exploited to enhance the response to ICB. We have extended these studies and mapped the expression of all human GPCRs in millions of tumor infiltrating lymphocytes and myeloid cells in >26 different cancer types using a novel large-scale scRNAseq integration pipeline. The emerging tumor-immune GPCR atlas may provide a valuable resource to explore the role of GPCRs in cancer immunology, and reveal new and exciting GPCR therapeutic targets to enhance the response to ICB. As a multipronged approach, we have also built on this scRNAseq integration computational approach to identify druggable oncogenic signaling networks that override cancer immune surveillance. We have focused on head and neck squamous cell carcinoma (HNSCC), an aggressive cancer type characterized by limited responses to ICB (<20%). Evidence will be presented that disruption of specific HNSCC driving signaling axes is sufficient to sculp the tumor immune microenvironment and disable their immune evasive mechanisms, thereby providing opportunities for the development of new multimodal precision immunotherapies for HNSCC and many other cancer types.

Biography

Dr. Gutkind's research team is exploiting the emerging information on dysregulated signaling circuitries and individual genomic and molecular alterations to develop new precision cancer therapies and multimodal immunotherapies. His team has pioneered the study of G proteins and G protein coupled receptors in human malignancies, and discovered that aberrant activation of the PI3K-mTOR network is the most frequent dysregulated signaling mechanism in oral cancer. He was elected to the National Academy of Medicine (2019) and named American Association of Cancer Research Professor (2023), reflecting his team's efforts on cancer signaling and his translational program to prevent and treat human malignancies.