Combination immunotherapy

Combination immunotherapy refers to the use of multiple immunotherapeutic agents or approaches simultaneously to enhance the immune system's ability to recognize and eliminate cancer cells or other disease-causing agents. Immunotherapy is a type of treatment that harnesses the body's own immune system to fight diseases, including certain types of cancer.

There are different ways in which combination immunotherapy can be approached:

Checkpoint Inhibitors Combination: Checkpoint inhibitors are drugs that block specific proteins (such as PD-1, PD-L1, or CTLA-4) on immune cells, allowing them to better attack cancer cells. Combining different checkpoint inhibitors or using them in conjunction with other treatments like chemotherapy or radiation therapy is one approach.

Combining Immunotherapy with Targeted Therapy: Targeted therapies focus on specific molecules involved in the growth and survival of cancer cells. Combining targeted therapies with immunotherapy can enhance the overall effectiveness of the treatment.

Vaccine-Based Therapies: Cancer vaccines can stimulate the immune system to recognize and attack cancer cells. Combining vaccines with other immunotherapies or conventional treatments is an area of active research.

CAR-T cell therapy with Checkpoint Inhibitors: Chimeric Antigen Receptor T-cell (CAR-T) therapy involves genetically modifying a patient's own T cells to express receptors that target cancer cells. Combining CAR-T cell therapy with checkpoint inhibitors aims to improve the persistence and efficacy of CAR-T cells.

Combining Different Immunomodulators: Besides checkpoint inhibitors, there are various other immunomodulatory agents that can be combined to enhance the immune response.

The rationale behind combination immunotherapy is to target multiple aspects of the immune system or cancer biology simultaneously, thereby increasing the chances of a durable and effective response. However, combining therapies also introduces challenges, such as increased potential for side effects and the need to carefully manage the sequence and timing of treatments.

Clinical trials are ongoing to evaluate the safety and efficacy of various combination immunotherapy approaches, and research in this field continues to evolve rapidly. It's important to note that the specific combination used may vary depending on the type of cancer, the patient's individual characteristics, and the stage of the disease. Patients considering or undergoing combination immunotherapy should discuss the potential benefits and risks with their healthcare team.

Combination immunotherapy holds promise for improving survival in responsive glioblastoma (GBM) patients. Programmed death-ligand 1 (PD-L1) expression in immune microenvironment (IME) is the most important predictive biomarker for immunotherapy. Due to the heterogeneous distribution of PD-L1, post-operative histopathology fails to accurately capture its expression in residual tumors, making intra-operative diagnosis crucial for GBM treatment strategies. However, the current methods for evaluating the expression of PD-L1 are still time-consuming.

Objective: To overcome the PD-L1 heterogeneity and enable rapid, accurate, and label-free imaging of

PD-L1 expression level in GBM IME at the tissue level.

Methods: We proposed a novel intra-operative diagnostic method, Machine Learning Cascade (MLC)-based Raman histopathology, which uses a coordinate localization system (CLS), hierarchical clustering analysis (HCA), support vector machine (SVM), and similarity analysis (SA). This method enables visualization of PD-L1 expression in glioma cells, CD8+ T cells, macrophages, and normal cells in addition to the tumor/normal boundary. The study quantified PD-L1 expression levels using the tumor proportion, combined positive, and cellular composition scores (TPS, CPS, and CCS, respectively) based on Raman data. Furthermore, the association between Raman spectral features and biomolecules was examined biochemically.

Results: The entire process from signal collection to visualization could be completed within 30 minutes. In an orthotopic glioma mouse model, the MLC-based Raman histopathology demonstrated a high average accuracy (0.990) for identifying different cells and exhibited strong concordance with multiplex immunofluorescence (84.31%) and traditional pathologists' scoring ($R2 \geq 0.9$). Moreover, the peak intensities at 837 and 874 cm-1 showed a positive linear correlation with PD-L1 expression level.

Conclusions: This study introduced a new and extendable diagnostic method to achieve rapid and accurate visualization of PD-L1 expression in GBM IMB at the tissular level, leading to great potential in GBM intraoperative diagnosis for guiding surgery and post-operative immunotherapy [1)]

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Zhou QQ, Guo J, Wang Z, Li J, Chen M, Xu Q, Zhu L, Xu Q, Wang Q, Pan H, Pan J, Zhu Y, Song M, Liu X, Wang J, Zhang Z, Zhang L, Wang Y, Cai H, Chen X, Lu G. Rapid visualization of PD-L1 expression level in glioblastoma immune microenvironment via machine learning cascade-based Raman histopathology. J Adv Res. 2023 Dec 8:S2090-1232(23)00377-6. doi: 10.1016/j.jare.2023.12.002. Epub ahead of print. PMID: 38072311.

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