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Short Commentary

Surgery and Specimen Biobanks -Tumor Tissues and Precision Medicine

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Introduction

Tumor disease is one of the most common causes of death in the world. Once the tumor is removed during the surgery, in the early periods, the solid tumor tissues are considered waste that is thrown away after excision and pathological diagnosis in most clinical hospitals. After 1994, we studied tumor tissue with Research and Development (R&D) for cell separation and storing techniques for tumor cells and immune cells, such as Tumor-Infiltrating Lymphocytes (TILs) from the tumor tissues. That time, we re-utilized tumor tissues for the treatment purposes of clinical patients; for example, the cultured TILs are activated and then infused into patients for adoptive immunotherapy while the primary tumor cells from tumor tissues are utilized as in vivo and in vitro chemosensitivity tests for chemotherapy. We also reported a combination therapy for patients with solid tumors by TIL re-infusion and chemotherapy using an in vitro chemosensitivity test as Figure-1.

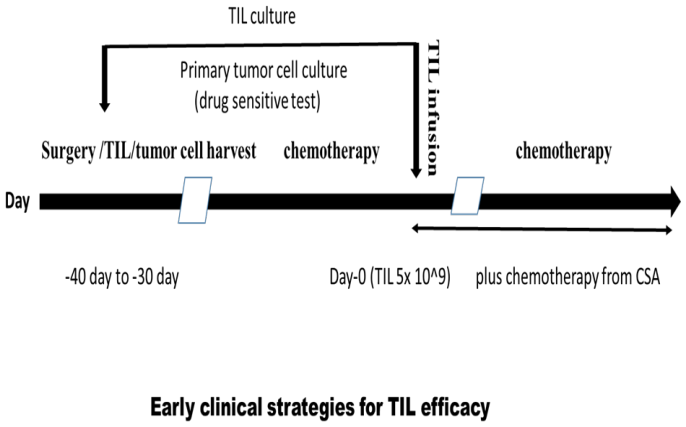


Figure 1: Tumor tissues related to our old version for both TIL immunotherapy and chemotherapy.

We found the combination was better than the single-agent treatment [1]. Following thirty years of research on tumor tissues after tumor removal concerning tumor tissue biobanks [2], single cell technique [3], clinical genomics [4], and artificial intelligence [5], a new generation of techniques is called precision medicine from tumor tissues after tumor removal during surgery. The latest generation of tumor tissue reutilization is more specific and sensitive to treating tumor disease than the old version by clinical genomic and single-cell techniques.

The New Techniques from Tumor Tissues Related to Precision Medicine

Tumor cells from tumor tissues are one of the largest populations in solid tumor tissues, which include Cancer Stem Cells (CSC) and later heterogeneous tumor cells containing their tumor antigens, which have been recognized by the corresponding and specific immune cells or lymphocytes, and finally metastatic tumor cells with spreading other tissue and organ. According to tumorigenesis related to genetic changes, it starts with subtle changes in the genetics called driver genes. Furthermore, the accumulation of driver gene changes will produce changes in tumor proliferation genes. Finally, tumor metastasis genes will result in tumor metastasis. After tumor removal, a successful sampling is discovered to have a set of driver genes, tumor proliferation genes, and maybe later tumor metastasis genes according to the update strategy. Once we study removed tumor tissues with different biomarkers in DNA level (SNP and epigenetics), RNA level (microRNA, picoRNA, non-coding RNA), and protein level in individual subjects [6], we can develop precision medicine as Figure-2A. As Figure-2A demonstrated, at least four fields can be involved in precision medicine after we have harvested a set of targeting genes.

A. Molecular Targeting Therapy Harvested from Tumor Tissue

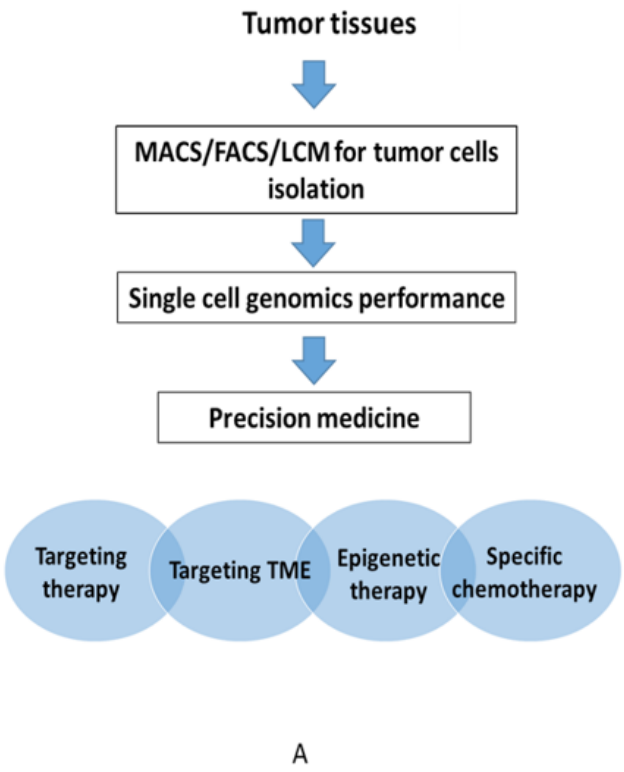


Figure 2A: Tumor tissues related to precision medicine: the protocol can be managed by precision medicine at prediction, prevent, prognosis and personalized therapy.

Molecular targeted therapies are advanced therapeutic techniques that interfere with specific molecules to block cancer growth, progression, and metastasis. Now, molecular targeted therapies approved by the Food and Drug Administration (FDA) have demonstrated remarkable clinical success in the treatment of a myriad of cancer types, including breast, leukemia, colorectal, lung, and ovarian cancers. Per our previous publications, here is an update on the different molecularly targeted therapies used in cancer treatment [7].

B. TME Targeting Gene from Tumor Tissue

Tumor Microenvironment (TME) and tumor cells in tumor tissue take many strategies to evade the host immune response by creating many immune-suppressive factors. Thus, we can use the strategy from TME to be personalized therapy. TME consists of tissues, cells, and signaling molecules in tumor tissue, affecting the immune response to tumor cells. Furthermore, TME elements of tissues, cells, and molecule factors include those during the early period of tumor tissues and those in an aggressive period in tumor tissues. Identifying and regulating TME cells and regulating molecules with their therapeutic agents is primarily reported. For example, Extracellular Matrix (ECM) and pathways such as Adenosine (ADO) and Indole-2,3-Dioxygenease (IDO) with their therapeutic agents may guide a new generation of precision medicine.

C. Epigenetics Targeting for Tumor Cells

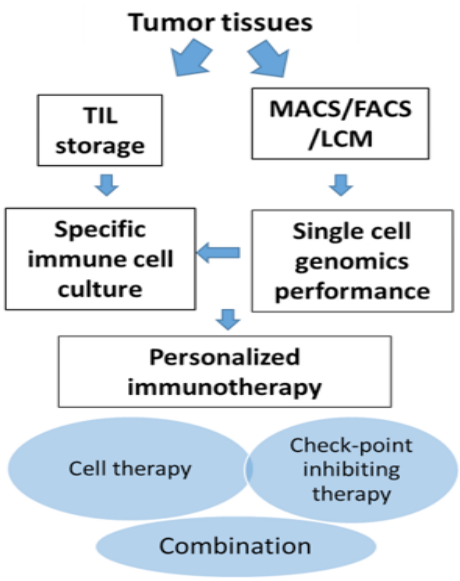
Epigenetic therapy is based on methylation assay and PTM histone assay. Methylated cytosines recruit protein complexes that promote functionally inactive heterochromatin under a global decrease in DNA methylation. However, DNA methylation is increased in silencing tumor suppressor genes that control cell growth, which can be removed by agents such as 5-Azacitidine (AZA) and Decitabine (DEC) by inhibiting DNMT1. Epigenetic therapy based on PTM histone assay is HDAC inhabitation, which removes the acetyl groups from the lysine residues, leading to the formation of a condensed and transcriptionally silenced chromatin. In recent years, there has been an effort to develop HDIs as an option for tumor treatment. Because HDI inhibiting HDAC has very good toxicity to tumor cells, currently, several HDIs are applied for hematological malignance and breast and lung cancers after tumor cell analysis.

D. Specific Chemotherapy of Tumor Cells

Personalized medicine, also referred to as precision medicine, is a new medical model to be directly tailored to the care of individual patients. A rational clinical genomic analysis to discover clinical genomic expression along with system modeling has been increasingly applied for personalized therapy. Customized chemotherapy has now been brought forward to the field of cancer. According to the protocol of personalized chemotherapy from tumor tissue, analyzing mRNA genomic expression level with its diagnosis, discovering gene expression signature by system modeling, and uncovering sensitive drugs from drug banks for clinical application.

The New Techniques from Tumor Tissue Related to Personalized Immunotherapy

In the early period, TILs are to be subject to clinical applications by cultured TIL infusion in vivo for Adoptive Cell Therapy (ACT). After twenty-five efforts, we used single-cell genomics analysis to discover a quiescent status from TIL [8], that is a group of upregulated quiescent genes such as Tob, LKLF, TGF-β, ERF, and REST/NRSF from a solid tumor [9]. Moreover, after thirty years' effort, we know that TIL is a group of heterogeneous immune cells so that we can perform ex vivo TIL quiescent analysis for determining immune characteristics to kill autologous tumor cells and then treat the tumor patients based on immune characteristics for the tumor diseases. Now we can measure quiescent status in the heterogeneous immune cells such as CD3+ T-cell (CD8+ T-cell and CD4+ T-cell), CD19+ B-cell (tumor-infiltrating B-cells, TIL-B), CD16+/CD56+ NK cell (Natural killer Cell), CD16+/CD56+/CD3+ NKT cell (Natural Killer T-cell), and other immune-cells (macrophage and neutrophil) [10]. After measuring, we can culture the specific group of immune cells for personalized immunotherapy. In detail, as shown in Figure-2B, for example, CD8 cells are in quiescent status, and CD8+ T-cells in TIL are cultured for personalized immunotherapy. Finally, the specific immune cells from TILs that have been specifically contacted to correspond with the tumor antigen of tumor cells will be cultured for precision immunotherapy. As we all know, TIL can recognize the tumor antigens on the surface of tumor cells with memory and then further move, migrate, and infiltrate tumor location to kill autogenous tumor cells after being cultured and infused back into patients. Furthermore, as Figure-2B, if we discover higher expression of checkpoint inhibiting molecules such as PD-1, which blocked immune cells, we can also further stimulate immune cells with PD-1 inhibitor to combine with the specific immune cells to personalized immunotherapy.



B

Figure 2B: Tumor tissues related to precision immunotherapy: the protocol can be managed by personalized immunotherapy.

Conclusion

Since 1994, we have studied cell separation and storage techniques for both tumor cells and immune cells from removed tumor tissues. Now, the new generation of precision medicine techniques combined with clinical genomics and single-cell techniques is more specific and sensitive to treating tumor disease than the old model with TIL infusion and in vivo and in vitro chemosensitivity tests for chemotherapy from removed tumor tissues.

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