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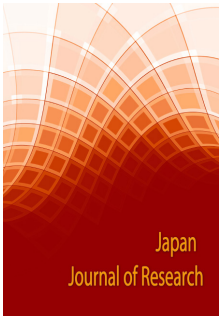

Precision Medicine Related to Landscape and Architecture of Tumor Specimen

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Abstract

After we reported the use of fresh tumor tissues removed surgically for therapeutic purposes in 1994, the removed tumor tissues have been largely applied for clinical treatment from a level of fresh tissues, level of frozen tissues until the level of pathological slides. Because the cell components from fresh tumor tissues are easier to culture than those frozen in liquid nitrogen tanks, both primary tumor cells and fresh immune cells from fresh tumor tissues are going to be increasingly researched for clinical applications, including precision medicine. This article will focus on the current progress of the landscape and architecture of freshly resected tumor tissues for precision medicine. Relying on the increasing reports of precision medicine, this article aims to report the landscape and architecture of tumor tissues for precision medicine of tumor diseases. This manual introduces the landscape and architecture of fresh tumor tissue gross specimens, the landscape and architecture of 3-D tumor tissue culture, the landscape and architecture of TME in tumor tissues, and finally, the landscape and architecture of tumor tissues can combine with single-cell technology, clinical genomics, and artificial intelligence so that the tumor tissue landscape and structure with clinical genomics and single-cell technology will allow us to find more specific and sensitive treatment for tumor diseases than our earlier established model of TIL infusion and ex vivo chemotherapy sensitivity testing (CST) from the resected tumor tissue.

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Keywords

Surgical specimens; fresh tumor tissue; adoptive cell therapy (ACT); landscape and architecture of tumor specimens; precision medicine; personalized immunotherapy; chemotherapy sensitivity testing (CST); tumor microenvironment (TME); and tumor immune microenvironment (TIME).

Introduction

In a very early, after a removed solid tumor tissue was applied for pathological diagnosis, the excision tumor tissue was considered waste and thrown away [1]. In early 1994, we reported a re-utilization of the fresh tumor tissues for treatment purposes after surgery removal of tumor masses [2]. For example, cultured tumor-infiltrating lymphocytes (TILs) from fresh tumor tissues are infused into patients for adoptive cell therapy (ACT). In contrast, the fresh primary tumor cells are employed as ex vivo chemosensitivity tests (CST) for chemotherapy from the removed fresh tumor tissues. In 1999, we further reported "Tumor tissue recycling--a new combination treatment for solid tumors: experimental and preliminary clinical research" in vivo journal [3]. Since then, fresh tissues from surgical removal have been increasingly applied for those at a level of fresh tissue and those at a level of frozen tissue stored in liquid nitrogen tanks for clinical subjects [4-5]. Fresh tissue can be traditionally used for TIL isolation and culture for ACT and is now newly used to study immune characteristics for the heterogeneous cell population within fresh tumor tissues for specific immunotherapy or optimizing combination therapy [6]. Because cell components from fresh tumor tissues of surgical removal are more easily cultured than those frozen in liquid nitrogen tanks, both the fresh primary tumor cells and fresh immune cells from fresh tumor tissues are increasingly applied for precision medicine.

Although frozen tumor tissue/cells stored in liquid nitrogen tanks are largely reported in precision medicine, such as single-cell sampling, single-cell genomics, and machine-learning modules in our laboratory or other colleagues [7-12], this manual will focus on the current advances to studying landscape and architecture from directly fresh tumor specimens of the removed tumor tissues for precision medicine. Relied on the increasing reports for precision medicine, the paper aims to report the landscape and architecture of tumor tissues, 3-D spherical tissue, and tumor microenvironment (TME) for precision medicine to treat tumor disease. The manual includes four parts: (1) The landscape and architecture of gross specimens from fresh tumor tissues; (2) The landscape and architecture of 3-D tumor tissue culture; (3) The landscape and architecture of TME from tumor tissues; (4) Precision medicine related to landscape and architecture of the fresh or culture tumor tissues.

The landscape and architecture of gross specimens of fresh tumor tissues

There is no consensus on how to achieve immune cells or primary tumor cells from fresh tumor due to the different tumor diseases and stages, distinct growth types, and different

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subjects achieved from fresh tumor tissues. However, the landscape and architecture of tumor tissues have been brought to the forefront from recent developments in fresh tumor cell harvest and culture, advanced immunotherapy, and current studies of TME [13-15].

Even if great individual differences are observed from fresh tumor tissues of different tumor diseases, different stages, and growth types, and different subjects after tumor mass removal, when the masses are dissected, several layers of a tumor mass still can be noticed from the removed masses. Typically, three zones are considered as: (A) necrotic center (necrosis), (B) invasive margin (infiltrating), and (3) peripheral stroma with tumor cell invasion as Figure 1 [16]. The necrosis is the innermost zone or layer composed of dead tumor cells due to inadequate blood supply and rapid proliferation. The infiltrating margin is a zone immediately surrounding the necrosis, where the tumor cells are actively migrating out of the surrounding tissue while infiltrating immune cells migrate into tumor mass to display an attack tumor cell. The outermost layer is the peripheral stroma, where tumor cells may be dividing and interacting with the surrounding tissue matrix, potentially further invasion, indicating further spread or metastasis. The three layers can be very changeable depending on the type of cancer, its stage and growth type, and subjects. The presence of cell components, which will be applied for precision medicine discussed below, can be harvested in the different layers, but they also will be varied on blood vessels, immune cell infiltrates, and stromal in the tumor environments.

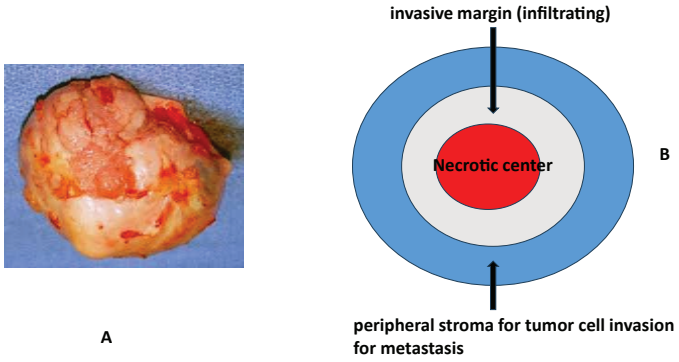

***Figure 1**. Landscape and architecture of gross tumor tissues. **A** means fresh tumor tissue landscape and **B** is landscape and architecture of dissected tumor tissues.*

Landscape and architecture of culturing tissue model

Over several decades, the landscape and architecture of cultured tumor tissues have been increasingly studied by a spherical body culture from tumor cells. A "spherical body culture of tumor cells " refers to a 3-D cell culture technique where cancer cells are grown in suspension, forming spherical structures called "spheroids" or "tumor spheres," which allows researchers to study tumor landscape and architecture for tumor cell behavior to compare to previous traditional monolayer cultures [17-20]. Theoretically, three stages are enveloping from avascular tissue, vascular tissue with angiogenesis into invasion tissue. Moreover, there are three zones in the avascular stage: (A) necrotic center (necrosis), (B) quiescent cells, and (3) active tumor cells (invasion) as Figure 2 [21]. However, there are differences among distinct tumor cells and tumor cell stages from cultures. The inner core is formed as a mass of dead cells due to insufficient nutrients. The outermost zone

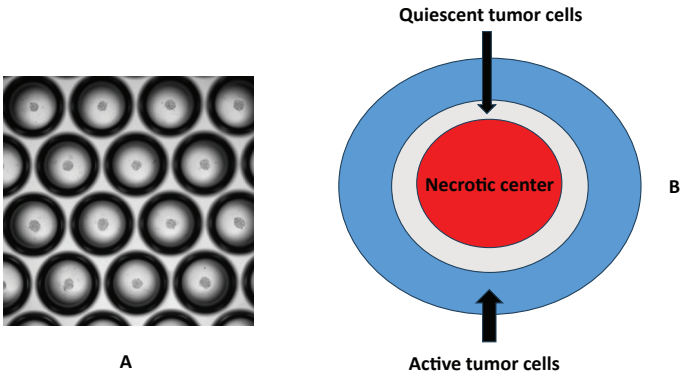

***Figure 2**. **Landscape and architecture from spheroid tumor tissue culture: A** means spheroid tumor tissue of plate-culture and **B** landscape and architecture from spheroid tumor tissue culture.*

consists of active tumor cells proliferating and infiltrating the surrounding. If immune cells are proliferating in the tissue model, macrophage, Natural Killer (NK) cells, and Cytotoxic T Lymphocyte (CTL) cells can be studied for immune behavior. The landscape and architecture of the tissue model can be applied to precision medicines in ex vivo. For example, the presence of cellular components can be assayed by compound responses, immune responses, and mathematical analysis for artificial intelligence (AI). Although the modules can be studied for immune cell infiltrating and stromal with tumor cells in the tumor environments, the modules of three stages and three layers also vary in the type of cancer, its stage, and its origin.

Landscape and architecture of tumor microenvironment

TME plays an essential role in discovering inhibiting compounds in tumor tissue. TME consists of three types of components according to our previous report: (A) tissue components called extracellular matrix (ECM) with epithelium, basement, and endothelium; (B) cell components including tumor-associated macrophages (TAM), neutrophils, carcinoma-associated fibroblasts (CAFs), myeloid-derived suppressor cells (MDSC) and so on; (C) signaling molecules affecting tumor growth by releasing extracellular signals, promoting tumor angiogenesis, inducing immune quiescence and increasing the growth of tumor cells as Figure 3A [22-25].

Recently, to study the TME mechanism, the landscape and architecture of TME can be classified into six specialized microenvironments: hypoxic niche, immune microenvironment, metabolism microenvironment, acidic niche, innervated niche, and mechanical microenvironment. This description can help clinical scientists create vivid landscapes and architectures from cancer biology to treatment [26].

Moreover, pathologists also classify TME as six layers to assess the potential aggressiveness to study inhibiting compounds for the TME interactions for different therapeutic compounds as Fig-3B [27]. The six layers include: (I) a tumor cell only in a core; (II) a niche; (III) confined; (IV) proximal; (V) peripheral; and (VI) organismal tumor environment. The core is a tumor cell-only environment called TCTCE (Tumor Cell to Tumor Cell Environment). A TCTCE core demonstrates cell death caused under a hypoxia condition, while the core edge shows tumor cells proliferating out by a higher oxygen called “metabolic symbiosis." Niche is the second zone for the local environment to tumor growth, although niche itself is used in

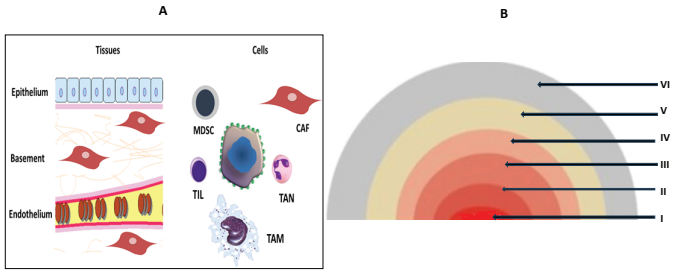

***Figure 3. Landscape and architecture from TME**: A means components of TME components and Fig-3B landscape and architecture with six layers of TME.*

a variety of contexts from different tumor types. Confined TE, proximal TE, and peripheral TE consist of multiple elements, although it is not clear that the components are essential to the TME. For example, the lymphatic vessel's components located more distally may not be considered as a part of TME. TOE (The tumor biological environment) indicates that the "organism" may have behavior for tumor progression. These six layers demonstrated tumor-promoting or tumor-suppressing mechanisms that we can apply to precision medicine. The complex layers can demonstrate a tumor cell process from tumor cell formation, tumor cell development, invasion, and finally metastasis so that they can apply for precision medicine regarding diagnosis and treatment with stages under AI.

Precision medicine under landscape and architecture of tumor tissue

We have conducted thirty years of research on tumor tissues, including tumor tissue biobanks, single-cell techniques, clinical genomics, and artificial intelligence [28-30]. A new generation of medical techniques is going to emerge for precision medicine. The latest generation of tumor tissue applications for precision medicine includes (A) Precision medicine under components and achievement such as tumor cell and immune cells in tumor tissue; (B) Studying tumor cell and immune cell components based on spherical body for therapeutic targeting; (C) Cellular distribution in TME for studying therapeutic targeting and (D) Precision medicine from information of landscape and architecture of tumor tissue.

Precision medicine by cell components in tumor tissue

As described above, there is no consensus on achieving immune cells or primary tumor cells because different tumor diseases, stages, growth types, and patients' subjects are different from fresh tumor tissues. However, precision medicine can use the landscape and architecture of tumor tissues with cell component distribution in tumor tissue. For example, we have reported TIL isolation and culture optimal harvested from fresh tumor tissues. As previously reported, after removing the inner zone composed of dead tumor cells and cutting off peripheral stroma (outermost layer) with tumor cell invasion, TIL proliferation, and activity CTL is much better than in other zones as Figures 4A and 4B [31-35].

Cell components based on spherical body for therapeutic targeting

As described above, the tumor spheres have three zones in the avascular stage at 3-D cell culture: necrotic center, quiescent cells, and active tumor cells at the outer core feature with proliferating and infiltrating features. The landscape and architecture of the tissue model can be applied to precision

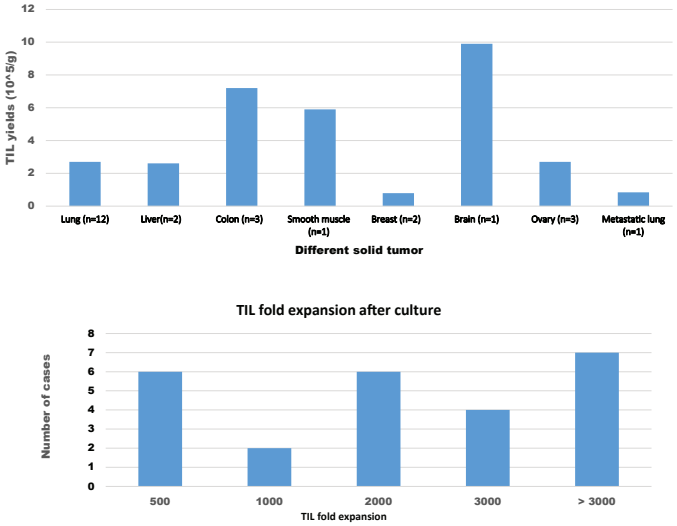

***Figure 4. TIL yields from zone-II of fresh tumor tissue:** A means TIL yields and **B** is TIL expansion fold from zone-II.*

medicines with ex vivo measurement for compound responses and immune responses. Moreover, tumorsphere cultures can be used to screen the drug pattern to achieve physiologically relevant efficacy and toxicity data from compounds from bench to the bedside, and finally discover new compounds for drug-resistant metastasis for patients so that precision therapeutic targeting selection is a reality. Furthermore, sphere cultures of tumor tissues combineed machine-learning algorithms make decisions to select compounds under AI analysis [41-45].

TME for studying therapeutic targeting

TME can divide three components as described, six classifications due to the TME mechanism, and six layers due to pathologist analysis. These six different layers demonstrated tumor-promoting or tumor-suppressing mechanisms that we can apply to precision medicine. For example, different components, six mechanism classifications, and six landscape layers of TME can be studied to progress or stages of tumor development, to discover and define compounds from drug banks for specific targeting from TME so that TME also can make specific therapeutic selection as reality. Furthermore, TME also can combines machine-learning algorithms to study a tumor cell process from tumor cell formation, tumor cell development, invasion, and, finally, metastasis so that TME landscape and structure can support precision medicine regarding diagnosis and treatment under AI [46-50].

Precision medicine from landscape and architecture of tumor tissue

Tumor cells from tumor tissues are one of the largest populations in tumor tissues, which include cancer stem cells (CSC) and later heterogeneous tumor cells, while immune cells are the largest populations to control tumor cell growth by spreading other tissue and organs [51-55]. According to tumorigenesis related to genetic changes, the landscape and architecture of tumor tissue may demonstrate subtle changes in genetics and genomics [56-60]. After tumor removal, a successful sampling consists of a set of driver genes, tumor proliferation's genes, and maybe later tumor metastasis genes so that we can develop precision medicine. As Figure 5 demonstrated, at least five fields can be involved in precision medicine after we have harvested a set of targeting genes from fresh tumor tissues.

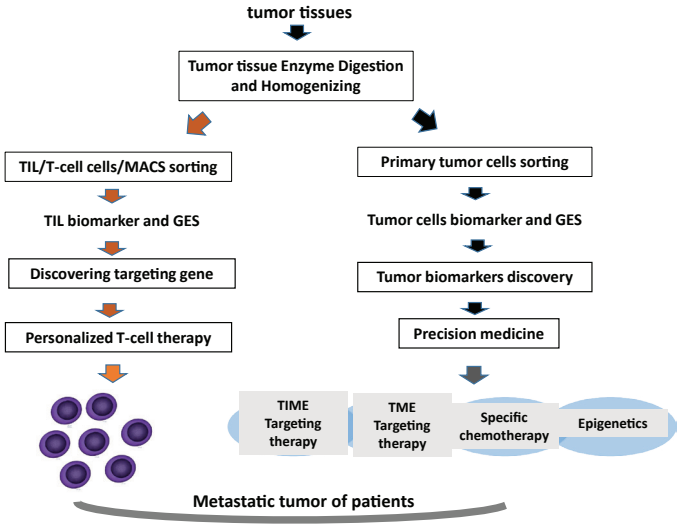

***Figure 5**. Tumor tissues related to precision medicine and immunotherapy*

***Table 1**. Antibody and small molecule targeting of TME*

Antibodies and kinase inhibitors	Targets
Gefitinib	EGFR
Afatinib	EGFR
Cetuximab	EGFR
Matuzamab	EGFR
Panitumumab	EGFR
Nimotuzumab	EGFR
Erlotinib	EGFR
Ponatinib	FGFR1
Dovitinib	FGFR2
Dovitinib	PDGFR
Sunitinib	PDGFR
Sorafenib	PDGFR
Ponatinib	PDGFRα
Aflibercept	VEGF-A
Bevacizumab	VEGFR
Ramucirumab	VEGFR2

Molecular targeting therapy for TME: Molecular targeted therapy is an advanced treatment technology that interferes with specific molecules to block the growth, progression and metastasis of cancer. Currently, molecular targeted therapies approved by the U.S. Food and Drug Administration (FDA) have achieved as Table-1 including breast cancer, leukemia, colorectal cancer, lung cancer and ovarian cancer [61]. Based on our previous publications, the following is the latest information on different molecular targeted therapies used in cancer treatment.

TIME targeting gene from tumor tissue: Tumor immune microenvironment (TIME) in tumor tissues will inhibit immune cell attack tumor cells. Therefore, we can use the strategies of immune checkpoint inhibitors (ICI) to block TIME for personalized treatment. TIME is composed of different compounds that affect the immune response to tumor cells. After the TIME identification from tumor tissues, if we discover higher expression of checkpoint inhibiting molecules such as PD-1, which blocked immune cells, we can use Pembrolizumab or nivolumab to inhibit PD-1 support personalized immunotherapy [62]. All ICIs are shown in Table 2.

***Table 2**. Immune checkpoint inhibitor*

Target	Agents
PD-1	Pembrolizumab, nivolumab, pidilizumab, MEDI0680, REGN2810, AMP-224, AMP-514
PD-L1	Durvalumab, atezolizumab, avelumab
PD-L2	rHIgM12B7
CTLA-4	Ipilimumab, Tremelimumab
LAG3	IMP321
OX40	MEDI6469, MEDI6383, MEDI0562, MOXR0916
GITR	TRX518
CD137	Urelumab
CD40	CP-870
CD27	Varlilumab

Epigenetics targeting for tumor cells: Epigenetic therapies are based on methylation assays and PTM histone assays. Methylated cytosines recruit protein complexes that promote functionally inactive heterochromatin in the presence of an overall decrease in DNA methylation. Now, tumor tissues removed can be measured for epigenetic targeting therapy such as 5-azacitidine (AZA) and decitabine (DEC), which inhibit DNMT1. PTM histone assays can be used for HDAC inhibition. In recent years, HDIs that inhibit HDACs can be routinely used for hematological malignancies. Now, several HDIs are currently being used for breast and lung cancer after epigenetic analysis from solid tumor tissues [63].

Personalized chemotherapy of tumor cells: Personalized chemotherapy has now been introduced into solid tumor disease. According to the customized chemotherapy regimen of tumor tissue, the mRNA genome expression level is analyzed and diagnosed, gene expression characteristics are discovered through system modeling, and sensitive drugs are found for solid tumor diseases such as in breast, digestive system cancer, and lung cancer to treat the solid tumor tissues [64].

Personalized ACT: Currently, we can measure the quiescent state in heterogeneous immune cells from heterogenous TIL, such as CD3+T cells (CD8+T cells and CD4+T cells), CD19+B cells (tumor-infiltrating B cells, TIL-B), CD16+/CD56+NK cells (natural killer cells), CD16+/CD56+/CD3+NKT cells (natural killer T cells), and other immune cells (macrophages and neutrophils). After measurement, we can culture specific immune cell populations for personalized ACT. For example, CD8 cells are in a quiescent state, and CD8+T cells in TIL are cultured for personalized ACT. Finally, specific immune cells that specifically contact tumor antigens of tumor cells are cultured from TIL for precision ACT [6].

In the near future, spheroid culture and TME can be developed for precision medicine of solid tumor disease if the landscape and architecture from spheroid culture and TME can discover sensitive and specific compounds ex vivo under AI.

Conclusion

Since 1994, we have studied fresh tumor tissue for cell separation and storage techniques, including tumor cells and immune cells from removed tumor tissues. Now, the new generation of precision medicine techniques requires an understanding of the landscape and architecture of tumor tissues. Understanding the landscape and architecture of tumor tissues combined with clinical genomics can find more specific and sensitive to treating tumor disease than the old model with TIL infusion and in vivo and in vitro CST for chemotherapy from removed tumor tissues.

Acknowledgments

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Competing interests statement

The authors declare non-competing financial interests.

Ethical approval

The two studies that are drawn upon for this article have ethics approval.

Informed consent

Informed consent (IC) was obtained from all study participants.

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