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Cancer Immunotherapy Using Microfluidic Systems

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Abstract:

Physicians are enthusiastic about using a novel approach known as cancer immunotherapy to address various forms of cancer. However, there are occasions when novel therapies that demonstrate efficacy in laboratory settings may not provide the same level of effectiveness when applied to actual patients. To address this issue, scientists are using miniature replicas known as microfluidic models. These models provide the examination of the interaction between cancer and immune cells in a manner that closely resembles the physiological conditions inside the human body. This review examines the role of microfluidic models in advancing the development of more effective cancer therapies. Let's begin by discussing the current state of affairs in cancer immunotherapy. Next, we explore the use of microfluidic models by scientists to gain insights into the mechanisms via which the immune system combats cancer and to evaluate the efficacy of novel therapeutic interventions. Additionally, we discuss the first measures used to demonstrate the efficacy of these models in predicting the effectiveness of therapies in human subjects. Lastly, we will discuss the advantages of using microfluidic models and the necessary steps to enhance their efficacy in the development of novel cancer therapies.

INTRODUCTION

Globally, cancer continues to be the primary cause of mortality, even with the widespread acceptance of numerous innovative treatments—certain of which have demonstrated enduring curative advantages. Recently, there has been a significant change in the way cancer is treated with the advent of cancer immunotherapy. This revolutionary plan utilizes the immune response to battle and potentially eliminate malignant cells, thereby transforming the chemotherapy landscape. Corresponding

with this, immunotherapy is presently a quickly expanding discipline in the medicinal management of cancer, with antibody-based and cell-based methods constituting the most prominent examples. Monoclonal antibodies (mAbs)., that attack checkpoint molecules or cancer-associated markers (e.g., CD20, EGFR, HER-2, CD38)., make up more than fifty per cent of the more than one hundred antibodies presently accessible for daily clinical use. This class of cancer (immuno).therapies is crucial and increasing rapidly (1).

Developments in antibody engineering have facilitated the production of new compounds based on antibodies that have specific effector activities or modified pharmacokinetics (2). Immune checkpoint-blocking antibodies, which commonly inhibit inhibitory receptors on T cells (e.g., PD-1 and CTLA-4)., have created considerable interest in the recruitment of patients' T cells to combat tumor cells (3). In addition to classical T cell-recruiting checkpoint blockers, immune-related checkpoints on myeloid effector cells that inhibit antibody-dependent cell-mediated cytotoxicity (ADCC). by neutrophils or antibody-dependent cellular phagocytosis (ADCP). by macrophages were also identified. Although the CD47/SIRPα axis represents the most notable and clinically advanced instance, there are currently antibodies in development targeting numerous other molecules. Among the various classes of molecules comprising antibody-based therapeutics, bispecific antibodies (BsAb). are presently experiencing substantial growth (4). Numerous BsAb bound to CD3 and antigens expressed by tumor cells, thus recruiting and activating T cells specifically. Conversely, BsAbs that bind to Fc receptors (e.g., those targeting FcγRI). were also rapidly tested in clinical settings and could potentially reappear as a novel method to recruit myeloid effector cells, including dendritic cells (DCs)., neutrophils, and macrophages (5).

Alongside bispecific antibodies and checkpoint blockers, chimeric antigen receptor (CAR).-transduced T cells are also considered a key component of authorized T cell-recruiting immunotherapies. Typical CAR constructions consist of an external single-chain antibody that is linked to intracellular activation domains (such as CD3ζ). and costimulatory domains (such as CD28 or 4-1BB) (6). CARs exhibit variations in the duration and strength of T cell activation, as well as their longevity in patients, depending on the signaling domains involved. The currently authorized target antigens for CARs include CD19 (four products). and BCMA (two products)., with the anticipation of more to come, such as CD22. The usual therapeutic indications mostly target blood cancers, whereas advancements in treating solid tumors are hindered by problems related to toxicity (7).

In addition to CAR T cells, additional modified cell products are being created, with encouraging outcomes in early clinical trials. As an alternative to CAR-T, engineered T cell receptor (TCR).-expressing T cells (TCR-T). have been proposed for solid tumor therapy. Baulu et al. examined recent clinical data for TCR-T treatments (8). Natural killer (NK). cells constitute an alternate cell therapy source that has the potential to overcome some of the drawbacks of CAR T, such as cytokine release syndrome and neurotoxicity. Currently, allogenic NK cell products are being studied in clinical studies, with encouraging findings in patients with acute myeloid leukemia and other hematological malignancies (reviewed by Berrien-Elliott et al) (9).

Aside from antibody-based and cell-based techniques, vaccinations against human papillomavirus and hepatitis B were effective in preventing cervical and liver cancer, respectively (10). Following the success of mRNA-based vaccinations in preventing Covid-19 infections, individualized therapeutic tumor vaccines show potential for treating pancreatic cancer (11). or melanoma (12). Furthermore, the use of modified oncolytic viruses capable of targeting and reproducing cancer cells while causing no harm to healthy cells has increased in recent years (13).

Microfluidics in biomedicine

Despite the considerable potential of cancer immunotherapies, the development of new ones continues to be a complex, time-consuming, and expensive endeavor, accompanied by a scarcity of approvals. Market analysts estimate that a solitary oncology agent could cost as much as $4.5 billion (14, 15). This necessitates the development of “fast failure” solutions which allow the early detection of ineffective medications or their repurposing (16). Due to the inadequate transfer value of preclinical models, which frequently neglect to faithfully replicate the human tumor microenvironment (TME)., the advancement of cancer immunotherapies is extremely expensive. In contrast to conventional two-dimensional cell culture models, which fail to incorporate critical attributes such as three-dimensional morphology, extracellular matrix, gradients, physiological oxygen levels, and vasculature, animal models have several drawbacks. These include inadequate productivity and turnover and high costs, a failure to dissect and regulate processes within the tumor microenvironment (TME)., and rodent models, in particular, possess immune systems that are significantly distinct from the human immune system (17).

Hence, microfluidic models provide a convincing substitute for conventional in vitro and animal models. These models provide a distinct benefit by faithfully reproducing intricate physiological microenvironments, while also allowing for dynamic and real-time examination of cellular responses. Furthermore, the natural capacity of microfluidic platforms to easily adjust in size, their decreased need for large sample sizes, and their capability for conducting experiments at a rapid rate make them very significant instruments for improving research in the field of biomedicine.

Microfluidics originated in the 1980s and is now a quickly advancing discipline that provides valuable tools for connecting traditional in vitro models with in vivo models. Microfluidics involves the manipulation of fluids on a very small scale, often in the range of tens to hundreds of micrometres. This is achieved using tiny systems that include linked channels, chambers, and reservoirs. This enables the manipulation of flow and molecule concentrations with greater precision by operating at low Reynolds numbers, resulting in laminar flow. The primary focus of biomedical research is to faithfully replicate the physiology of tissues in organs-on-chips, which is a crucial technology for developing tissue models that correctly simulate the 3D tissue environment (18).

Microfluidic devices can be manufactured using a variety of techniques and materials (e.g., etching, molding, soft lithography, 3D printing)., including silicon, plastic, paper, glass, and polydimethylsiloxane (PDMS).. PMADS continues to be the most extensively utilized material in the fabrication of microfluidic devices. PDMS is a readily accessible and inexpensive material. The material’s optical transparency facilitates on-chip high-resolution imaging, while its flexibility permits the fabrication of deformable elements and valves. Additionally, its biocompatibility and gas permeability establish it as an exceptional material for biomedical applications (19, 20).

However, a significant disadvantage of this material is its hydrophobic nature and its tendency to absorb

tiny biomolecules. As a result, researchers have been exploring and using other polymers including poly(methyl methacrylate). (PMMA).. Fang et al (19). recently conducted a comprehensive analysis of the manufacturing technologies that are often employed in tumor-on-a-chip systems.

Microfluidic devices enable a variety of functions, such as evaluating multiple variables, controlling gradients (including oxygen levels)., compressing and stretching the tissue, applying sheer stress and interstitial flow, and integrating sensors to measure physical and chemical properties (such as electrical signals, pH, and oxygen levels). These capabilities have been reviewed by Ko et al (20). and Palacio-Castañeda et al (21).

The combination of engineering and cell culture methods has led to the creation of microfluidic tumor models, often known as tumours-on-chips. These models provide a compartmentalized and more physiologically appropriate depiction of the tumor microenvironment (TME), which can be controlled. They are increasingly being employed for the development of immunotherapy. This research presents a summary of how the advancement of various sorts of immunotherapy (such as antibody- and cell-based treatments, cytokines, oncolytic viruses, and cancer vaccines). is enhanced by the utilization of microfluidic platforms. This text examines the potential, constraints, and future possibilities of using microfluidic models to produce cancer immunotherapies. It emphasizes the circumstances in which these models might aid in the translation of cancer immunotherapies from laboratory research to clinical application.

Development of cancer immunotherapy using microfluidic tumor models

In recent years, researchers have created and used many microfluidic tumor models to further the development of cancer immunotherapy. The majority of models consist of parallel channels, which typically include a tumor section containing a hydrogel that contains cancer cells or spheroids, as well as immune cells that are either embedded in a hydrogel or perfused from a side channel. The selection of the microfluidic model design is usually determined by the individual research topic being investigated. This is because the throughput, dynamic features (such as flow), and molecular readout options may vary significantly across different models. In this discussion, we will explore the latest uses of microfluidic models in the advancement of major forms of cancer immunotherapies.

T-cell immunotherapy

Microfluidic models are becoming essential for exploring T cell-based anti-cancer therapy. These models enable systematic studies of immune cell interactions and procedures for therapy.

T Cell-Based Monoclonal Antibody (mAb). Therapies

Breast and Colon Cancer: Jiang et al. created a high-throughput observation chamber (iHOC). to examine the impact of an anti-PD-1 antibody on T cells associated with breast cancer. This study showed that the antibody was able to counteract the suppression of T cells caused by PD-L1, increase the production of IL-2, and boost the ability of T cells to enter and survive inside the tumour microenvironment. Sehgal et al. used a commercially available microfluidic system to demonstrate that the combination of PD-1 blockage and Birc 2/3 antagonism enhanced the eradication of cancer cells in colon cancer spheroids (26, 27). Glioblastoma: Cui et al. developed a chip made of PDMS that combines patient-derived GBM cells with other immunological components. It was shown that combining PD-1 and CSF-1R inhibitors might effectively counteract immunosuppression in aggressive GBM, as evidenced by cytokine profiles that closely resembled those of actual patients (23).

Cell Therapies

Leukemia: Chen et al. constructed a microfluidic model that replicates a leukaemia niche to investigate CAR-T cell therapy. Their model precisely depicted clinical reactions, including remission, resistance, and recurrence. Additionally, it emphasised the aspects that contribute to the lack of success in therapy and proposed its use as a tool for pre-clinical trials (24).

Liver Cancer: Preece et al. used a three-lane chip model to evaluate the efficacy of TCR-engineered T lymphocytes against hepatoma cells. Their research demonstrated an increase in the production of cytokines and the ability of these modified T cells to destroy tumour cells, indicating the promising potential of these altered T cells (28).

Security and immune response to foreign cells Kerns et al. confirmed the validity of lung- and intestine-on-a-chip models for evaluating the safety of T cell bispecific antibodies (TCBs). Their models accurately forecasted the optimal time frames for effectively eliminating cancer cells while minimising injury to healthy organs, in line with the observed reactions in animal models. Although alloreactivity is a problem, the period and components used in these in vitro investigations often reduce this danger. To further reduce alloreactivity, it is important to ensure compatibility between HLA/MHC or use cells produced by the patient (29, 30).

Natural Killer (NK). Cell Therapies

Studying the actions of NK cells in microfluidic tumor models is essential for gaining valuable knowledge about their ability to fight cancer and their potential use in therapy.

Interaction between natural killer (NK). cells and cancer

Nguyen et al. and Marzagalli et al. investigated the function and characteristics of NK cells by using microfluidic models of colorectal cancer and neuroblastoma, respectively. Nguyen's model used functioning cardiac tissue to evaluate tolerability, demonstrating targeted tumor destruction by NK cells without inducing structural abnormalities, but also decreasing the beating rate of the heart tissue. Marzagalli's model specifically examined the process of NK cell migration and extravasation, demonstrating the selective recruitment of CD16-negative NK cells to neuroblastoma spheroids and subsequent induction of tumour cell death. These models play a crucial role in assessing the behaviour, movement, and effectiveness of NK cells in controlled settings (31, 32). Therapies use monoclonal antibodies to activate natural killer cells Gopal et al. employed a high-throughput microfluidic device to investigate the synergistic impact of trastuzumab (an anti-HER2 drug). and atezolizumab (an anti-PD-L1 drug). in combination with doxorubicin and/or paclitaxel on the ability of natural killer (NK). cells to destroy pancreatic and breast cancer cells. Their technique caused a state of low oxygen levels inside tumour spheroids and showed a decrease in the amount of chemotherapeutics needed to achieve 50% effectiveness when paired with NK cells and antibodies (33).

Ayuso et al. investigated the impact of atezolizumab and the IDO-1 inhibitor epacadostat on a breast cancer model taken from a patient. The model was created using a specially designed PDMS device. This chip used an endothelial cell-patterned channel to create a functioning vascular tube, while a hydrogel was used to construct nutrition and metabolite gradients. A study revealed that environmental stress hindered the functioning of NK cells, although this effect may be partly reversed by inhibiting PD-L1 and IDO-1 (34).

Additional monoclonal antibody therapies

Recent research has investigated the efficacy of monoclonal antibody (mAb). therapy in using additional types of effector cells, including patient-derived tissue-resident immune cells and monocyte-derived macrophages, in addition to T and NK cells.

Immune cells gathered from the patient

Ao et al. evaluated the efficacy of anti-PD1 antibodies in mouse and human mammary cancer models utilizing an ex vivo on-chip model that included patient-derived material. Their PDMS apparatus, which consisted of 960 flow units and 16 channels containing 60 wells each, enabled the examination of tumor aggregates in a high-throughput manner across 16 different treatment settings. The researchers assessed the vitality of cells, examined the inflammatory profiles, and analyzed the makeup of the tumor. The in vitro reactions of separated syngeneic murine mammary carcinomas precisely anticipated the in vivo reactions, but original tumor cells from patient-derived samples exhibited diverse reactions to PD-1 inhibition. Although there is no evidence of clinical response, this research confirmed the ability of on-chip models to predict preclinical results (33, 35).

Macrophages derived from monocytes

Researchers conducted a study on monocyte-derived macrophages in a breast cancer model called MDA-MB-468. They used a microfluidic technology that is suitable for high-resolution imaging and cytokine/RNA analysis to combine an anti-EGFR IgA with a CD47 checkpoint blocker. The combined treatment effectively stimulated M2 macrophages, leading to an enhanced ability to engulf cancer cells and an elevation in the production of pro-inflammatory cytokines TNFα and IL-6. Additionally, there was an upregulation of both M1 and M2 markers. This research emphasises the significance of macrophages in cancer immunotherapy (36).

Alternative Immunotherapeutic Methods

Microfluidic systems are used to investigate novel immunotherapies, such as cytokine targeting, oncolytic viruses, vaccinations, and RNA-based medicines.

Targeting Cytokines and Oncolytic Viruses

Targeting Cytokines: Es et al. conducted a study to examine the effects of pirfenidone (PFD)., a drug that inhibits fibrosis, on cancer-associated fibroblasts (CAFs). in a breast cancer model. They used a microfluidic chip with three lanes for their experiments. The administration of PFD resulted in a decrease in the production of immunosuppressive cytokines, leading to a reduction in both CAF and cancer cell migration and invasiveness (37). Mencattini et al. used the same framework to investigate the oncolytic properties of the vaccinia virus (OVV). in a lung cancer model. Their investigation using video-microscopy showed that immune cell recruitment was improved and immune-cancer cell contacts were extended, resulting in greater cancer cell death in the presence of OVV (38). Vaccines and RNA-based methods Kim et al. used bioprinting to construct a three-dimensional bladder model to examine the impact of the Bacillus Calmette-Guérin (BCG). vaccination. The administration of BCG therapy resulted in an augmentation in the production of inflammatory

cytokines and the migration of macrophages, suggesting a possible immunostimulatory impactn (39). Hong et al. used a PDMS-based chip to investigate the efficacy of miRNA-based treatment in a glioblastoma (GBM). model. The researchers discovered that extracellular vesicles (EVs). containing miRNA-124 effectively hindered the development and invasion of GBM (glioblastoma). cells. Additionally, these EVs repressed the polarization of M2 microglial cells, reduced the production of proteins that promote tumor growth, and facilitated the recruitment of NK (natural killer). cells. These findings align with the gene expression patterns seen in GBM cell lines obtained from patients (40).

Conclusions and Future Considerations

Microfluidic tumor models are transforming cancer immunotherapy by including functioning immune components to investigate treatments, namely monoclonal antibodies such as PD-1 inhibition (41). These models allow for accurate manipulation of microenvironmental circumstances and continuous monitoring of interactions between immune cells and tumor cells, providing useful insights for both established and innovative immunotherapeutic strategies. They show potential in enhancing the process of choosing patients and creating treatments that include several types of immune cells, such as NK cells and macrophages. Although there are benefits, there are still obstacles to overcome, like the complex process of manufacturing, the need for uniformity, and the verification of prediction accuracy. Future developments will prioritize enhancing model complexity by including more cell types and developing multi-organs-on-chip systems (42). Furthermore, efforts will be made to improve the regulation of oxygen and pH levels and to establish standardized techniques to facilitate wider implementation (21). By incorporating regulatory frameworks and the pharmaceutical industry's discovery pipeline, together with the use of in silico modelling, cancer immunotherapy research and development will be greatly advanced, leading to improved prediction capacities and considerable progress.

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