PharmaMedical Trend Analysis (PMTA)

Issue 2, Volume 1, September 2022

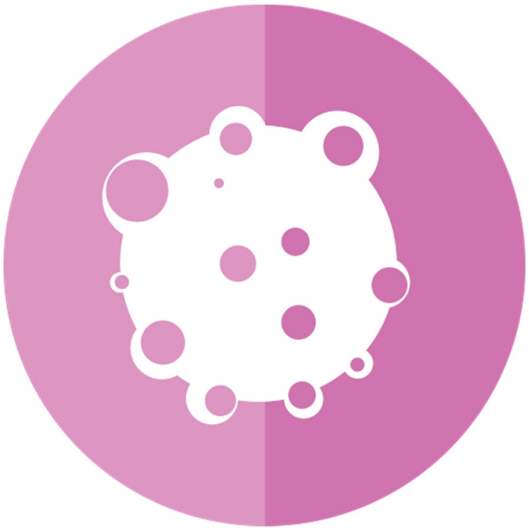
Contents

PMTA: Published by Ariban PublicationTech,
Queensland 4304, Australia
E-mail: ariban.pubtech@gmail.com
Tel: +61477071389
Website: https://www.pharmamedicaltrendanalysis.com/
Facebook: facebook.com/Ariban-PublicationTech

How do cancers and tumours evade the immunity? Current therapeutic options and future research

Dr Md Anawar Hossain

Cancer is one of the deadliest diseases causing very high death toll every day in the world. Frequently, cancer has a poor prognosis. Multiple therapeutic strategies and treatment options have been developed for various cancers and tumours. The chemotherapy, radiotherapy, targeted therapy, and immunotherapy are applied over the past several decades. However, resistance to these therapies is a major issue that impedes the clinical outcomes and effectiveness of cancer treatments and impacts patient survival. The patients with early stage positively respond to the treatments, but they poorly respond and show dire clinical outcomes at a later stage (Wu et al., 2021 and references therein).



Tumours, Structure and Immune System

The tumours produce tumour antigens that can enable the immune system to differentiate tumour cells from normal cells. Antigens trigger the immune response and activate the T cell response that can provide defense against tumourigenesis. But tumour cells develop some mechanisms to evade or avoid host immunity for their growth and survival (Spurrell and Lockley, 2014).

Tumours grow within a complex environment of structures, cells, and chemical signals ranging from epithelial cells, stroma, blood, and lymphatic vasculature, immune cells, cytokines, and chemokines. The structure of a typical tumour consists of the tumour core, the invasive margin, and the surrounding stromal and lymphoid components. Some components within the immune milieu are beneficial, while some components are deleterious to the patient. There are different immune cells identified in different locations within a tumour. The clinical outcome is presumed to be affected due to the variation in density and distribution of immune cells within tumours. The anti-tumour immunity can be increased by the down-regulation of immune checkpoint proteins. The antibodies are increasingly used to up-regulate host anti-tumour immunity with some durable results seen in early trials so far (Spurrell and Lockley, 2014).

What is Tumour Microenvironment?

The tumour microenvironment (TME) is the extracellular environment that contains tumours cells, carcinogenetic cells, cancer-associated fibroblast (CAFs), immune cells, the vasculature system, and the extracellular matrix (ECM) including secreted cytokine, chemokine, metabolites, and exosomes. The genetic and epigenetic alterations in tumour cells provide them active resistance capacity. Besides this, the tumour microenvironment (TME) plays a key role in tumorigenesis, metastasis,

progression, and adaptive resistance to cancer treatment (Wu et al., 2021 and references therein).

Adaptive Mechanisms of Cancer/Tumour Resistance

Wu et al. (2021) indicated that the adaptive mechanisms of tumour resistance are intimately related to tumour microenvironment. However, adaptive mechanisms driven by the TME are not yet clearly understood and need detailed studies to fully elucidate the mechanisms of tumour therapeutic resistance. But there are some evidences that many clinical treatments targeting the TME have been successful. Cancer cells escape from the cytotoxicity of tumour therapies through the following intrinsic mechanisms, e.g., decreased drug accumulation, altered drug metabolism, mutated, or altered drug target and enhanced DNA repair capability, as well as inactivated cell death signalling. Tumour cell heterogeneity is one of the factors that creates various resistance responses for multiple therapies. Sometimes, tumours progression continues, even though they face external pressure from various therapies. Therefore, new theories have proposed that tumour progression is a dynamic and complicated process that tightly interacts with the surrounding environment (Wu et al., 2021 and references therein).

The non-malignant cells in the TME actively boost carcinogenesis by promoting excessive tumour initiation, malignant progression, metastasis, and therapeutic resistance. The transformed cancer cells contribute extensively to tumour development and resistance by interaction with stromal cells in the TME. Some preclinical studies indicate that the TME is a potential therapeutic target (Jin and Jin, 2020). For instance, multiple strategies of combined therapy related to the TME have shown interesting potential (Wu et al., 2021 and references therein).

Tumours and Immunity Evasion

The development of tumours despite host immunity indicates that tumour cells develop immune avoidance. Tumours develop immunity resistance through several mechanisms (Wu et al., 2021 and references therein):

- Some tumours have been demonstrated to lose expression of MHC molecules making them unable to present tumour antigens, thus evading T cell recognition.
- Some tumours secrete immunosuppressive cytokines, e.g., IL-10.
- Some tumours generate physical barriers, e.g., collagen and fibrin, thus making them invisible to the immune system.
- Tumours can also evade the immune response by up-regulating inhibitory molecules and inducing a form of self-tolerance.
- An immune response can be produced by T cells depending on co-stimulatory signals. However, inhibition of co-stimulatory signals creates immune tolerance. Cytotoxic T-lymphocyte associated antigen 4 (CTLA4) and programmed cell death protein 1(PD1) are both inhibitory receptors involved in down-regulation of immune responses.

What is Immunotherapy

Immunotherapy is one kind of cancer treatment strategies that boosts the patient's own immune system to eliminate cancer cells in solid tumours (Xu et al., 2022). More than 70 FDA-approved immunotherapy drugs were available up to now at April 2022. A plenty of immunotherapy-related

clinical trials have been registered around the world for more than 50 types of cancers. Immunotherapy mainly includes cancer vaccines therapy, oncolytic virus therapy, dendritic cell (DC) therapy, adoptive cell therapy, antibody–drug conjugates (ADCs), and immune checkpoint inhibitors (ICIs). Out of these, ICIs, which use antibodies to programmed cell death protein 1 (PD-1) and programmed death ligand 1 (PD-L1) showed the most success (Xu et al., 2022). Although new technologies single-cell multi-omics may solve many problems, cancer immunotherapy still faces many challenges.

What is Tumour Immune Microenvironment?

Solid tumour tissue consists of highly heterogeneous cancer cells (Xu et al., 2022). The different upstream mutations and the tumour microenvironment (TME) form the variable compositions and evolutionary states of these cancel cells. The composition of TME controls the tumour–host interaction. Tumour immune microenvironment (TIME), compositing different cell groups of the immune system and their interactions in the TME niche significantly control the processes of carcinogenesis, cancer progression, and responses to the treatments (Xu et al., 2022).

What is Systemic Tumour Immune Environment (STIE)?

Systemic tumour immune environment (STIE) contains the immune modulating molecules and immune cells and mainly governed by the circulating blood and lymphatic vessels (Xu et al., 2022). It has significant role in communication between the primary tumour site to the distant organs and the host immune organs such as bone marrow and lymph nodes. The functional immune modulators are proteins, cytokines, and metabolites, while the immune cells comprise myeloid cell lineages (neutrophils, monocytes, megakaryocytes, platelets, basophils, eosinophils) and lymphoid cell lineages (T cells, B cells/plasma cells, and NK cells).

Relationship and Interactions between TIME and STIE

There are extensive interactions between tumour immune microenvironment (TIME) and systemic tumour immune environment (STIE). Investigation on the TIME of tumour in situ and metastatic sites, along with STIE in blood, plays a significant role to understand the mechanism of tumour progression and overall cancer treatment (Xu et al., 2022). Looking for the key factors in STIE and TIME may identify pathway to improve the treatment efficiency of PD-1 inhibitors. As more clinical trials continue, effective combination of radiotherapy and immunotherapy will continue to make great breakthroughs.

Multiple Strategies to Prevent Immune Resistance

Multiple strategies targeting the TME have been investigated to prevent resistance to radiotherapy, chemotherapy, and immunotherapy (Wu et al., 2021 and references therein).

- Cancer-Associated Fibroblasts (CAFs) is the most abundant cell type in the TME that have the critical role in therapeutic resistance of tumour cells. Therefore, targeting CAF functions is a promising approach for tumour therapy.
- It has been shown to be an efficient tumour therapy strategy to stop the communication between tumour cells and their environment by targeting adhesion molecules, proteolytic

enzymes, and ECM components.

- Different strategies can be used to target the immune system in TME and tackle cancers, because the immune system in TME influences the response of tumours to various clinical therapies.
- The low oxygen pressure and acidosis conditions in the TME affect a tumour's response to treatment. Therefore, manipulating hypoxia and acidosis conditions in the TME can stop tumour progression.
- Capturing and leading the TME to increase drug delivery can significantly increase the efficacy of chemotherapeutic drugs.

Reference

Spurrell E.L, Lockley M., 2014. Adaptive immunity in cancer immunology and therapeutics. ecancer https://doi.org/10.3332/ecancer.2014.441

Wu P, Gao W, Su M, Nice EC, Zhang W, Lin J, Xie N, 2021. Adaptive Mechanisms of Tumor Therapy Resistance Driven by Tumor Microenvironment. Front. Cell Dev. Biol. 9:641469.

Xu, L., Zou, C., Zhang, S. et al., 2022. Reshaping the systemic tumor immune environment (STIE) and tumor immune microenvironment (TIME) to enhance immunotherapy efficacy in solid tumors. J Hematol Oncol 15, 87. https://doi.org/10.1186/s13045-022-01307-2

Diabetic kidney disease: Use of metabolomics for the early diagnosis

Dr Md Anawar Hossain

Metabolomics and Its Use to Identify Early Stage of Diabetic kidney disease (DKD)

Metabolomics is one of the omics technologies that can detect metabolites in living organism. Metabolomics can determine complex metabolic networks in human body and give insight of several physiological or pathophysiological processes, that can identify the diseases' unique metabolic signatures. Thus, metabolomics is a promising tool that can not only detect metabolites but also identify pre-disease states for the early clinical practice and treatment. Therefore, the use of metabolomics as a tool can identify the DKD metabolic signature of tubule interstitial lesions to diagnose or predict the time-course of DKD (Pereira et al., 2022).

DKD leads to increasing urinary albumin excretion with a rise in proteinuria and a drop in estimated glomerular filtration rate (eGFR) in the absence of other renal diseases (Abdelsattar et al., 2021). The albumin to creatinine ratio (ACR) can determine renal function. But the muscle mass and the physical activity can affect the ratio due to the variable creatinine excretion in male and female, and the equations such as the Modification of Diet in Renal Disease (MDRD) used for the estimation of GFR. There are several drawbacks to the use of urine albumin. Therefore, a suitable biomarker is needed to identify the renal function. Abdelsattar et al. (2021) reported that dodecanoylcarnitines C12, triglylcarnitine C5:1, and isovalerylcarnitine C5 were stronger predictors of albumin/creatinine ratio than HbA1c and suggested them as potential biomarkers for the diagnosis of the early stages of DKD.

References

Abdelsattar S., Kasemy Z.A., Elsayed M., Elrahem T.A., Zewain S.K., 2021. Targeted metabolomics as a tool for the diagnosis of kidney disease in Type II diabetes mellitus, British Journal of Biomedical Science, DOI: 10.1080/09674845.2021.1894705

Pereira P.R., Carrageta D.F., Oliveira P.F., Rodrigues A., Alves M.G., Monteiro M.P., 2022. Metabolomics as a tool for the early diagnosis and prognosis of diabetic kidney disease. Medicinal Research Reviews, Vol. 42 (4), 1518-1544.

Significant impact of multimodal molecular imaging in drug discovery and development

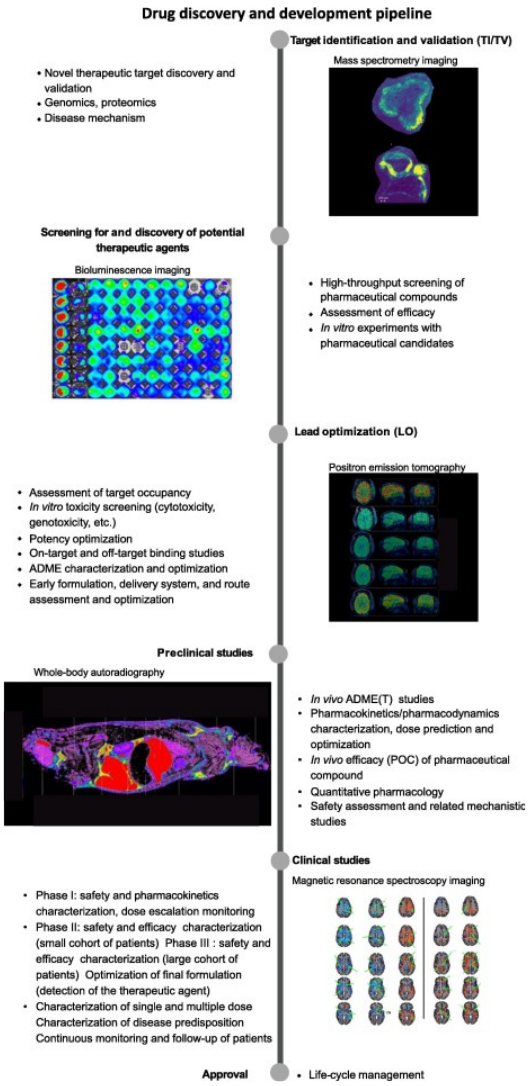
Dr Md Anawar Hossain

Drug discovery and development process

The drug discovery and development processes can be both time-consuming and costly. It generally takes 12 years from the discovery of a new molecular entity to regulatory approval before a drug enters the market (Vermeulen et al., 2022). Despite the high investment, sometimes some drug candidates do not reach the market. Therefore, the acceleration of drug development process is very important for the pharmaceutical industry.

What is multimodal imaging technique and its uses?

It is not only an individual imaging technique. It is the combination and integration of several imaging techniques which can provide large amounts of anatomical, functional, and molecular information in order to enhance drug discovery and development processes. The combination of these techniques helps to elucidate the mechanism of disease, discover new pharmacological targets, and assess new potential drug candidates and treatment response.



Multimodal imaging technique can help in various phases of the drug discovery and development (Fig 1). Multimodal imaging can provide additional spatial or molecular information. It helps informed decision-making and accelerate the drug discovery and development. Many compounds may have the undesirable properties in terms of their potency, pharmacokinetics or safety and these compounds can be eliminated earlier, which will reduce costs significantly in

later phases. Therefore, Vermeulen et al. (2022) reviewed the recent innovations, strengths, and the potential of imaging techniques and their multimodal application in preclinical research. They also reviewed how pharmaceutical research and development processes can be accelerated with artificial intelligence (AI) and radiomics applied to imaging data. Several significant benefits of multimodal imaging technique are discussed below:

1. Molecular imaging uses both targeted and untargeted approaches to image molecules at the cellular and subcellular level. Targeted approaches make an image of a specific drug molecule (e.g., distribution or metabolism) or a specific target (e.g., target occupancy).

2. This Imaging techniques can produce maps of known or unknown exogenous and/or endogenous compounds in the region of interest.

3. Different imaging modalities can be applied in pharmaceutical research to provide information about tissue pharmacokinetics, drug pharmacodynamics, and response of endogenous molecules (metabolites, lipids, and proteins) to the disease and the treatment.

References

Vermeulen I., Isin E.M., Barton P., Cillero-Pastor B., Heeren R.M.A., 2022. Multimodal molecular imaging in drug discovery and development. Drug Discovery Today, Vol. 27, Issue 8, Pages 2086-2099.

Quality and price of active ingredients and their impact on effectiveness and potency of medicine

Dr Md Anawar Hossain

- The good quality of active pharmaceutical ingredients (APIs) can ensure the manufacturing of the high quality, effective and safe essential drugs, while the use of low quality APIs can produce less effective and unsafe drugs.
- The price volatility of APIs can affect the small pharmaceutical companies.
- One potential way to address the above problems would be to broaden the WHO prequalification system and include APIs for drugs that are on the WHO model list for essential medicines.

Thermott tool to determine protein–ligand binding constant

Thermott is a web application for analysis of thermal shift assay (TSA)/ differential scanning fluorimetry (DSF) data (Gedgaudas et al., 2022). It is an online tool to determine the protein–compound binding constant from thermal shift data. It is a free, user-friendly and open-source online analysis software that provides estimates of the thermodynamic data on target proteins.

The thermal shift assay technique can determine protein–ligand affinities ranging from millimolar to picomolar levels in a single ligand dosing experiment. However, this technique is not widely used due to the complexity of thermodynamic data analysis. Therefore, Gedgaudas et al. (2022) have developed a user-friendly, open-source, free online analysis software to study any protein–ligand interaction thermal shift data and yield a comprehensive thermodynamic characterization of the binding reaction. The software can determine ligand binding strength to protein (K_b or K_d). The experiment is done by adding different ratios of ligand to protein. It can determine how different conditions (e.g., salts, metal ions, pH, etc.) influence protein stability. This technique is useful to determine optimal protein crystalization or storage conditions.

Reference

Gedgaudas M., Baronas D., Kazlauskas E., Petrauskas V., Matulis D., 2022. Thermott: A comprehensive online tool for protein–ligand binding constant determination. Drug Discovery Today, Vol. 27 (8), pp. 2076-2079.