EDITORIAL
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Tumour Microenvironment in Therapy of Metastatic Cancer

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Abstract: GLOBOCAN 2020 has reported that the global cancer burden is 19.3 million cases, with 10 million deaths[1]. The overall survival (OS) after treatment with innovative cancer therapies has not changed for most metastatic cancer patients, and more in-depth study is needed. Several studies have suggested that understanding the cellular and molecular mechanisms underlying metastatic processes can be used as a novel strategy to disrupt cancer cell pathways and contribute to the development of effective and safe therapies against metastatic cancer. Recent studies have shown that the tumour microenvironment (TME) is responsible for reprogramming tumour initiation, progression, invasion, and metastasis. Thus, TME probably hinders positive responses to innovative therapies. Therefore, clinicians must consider targeting major cell components associated with TME instead of only using presently available genomic profiles of tumours for effective treatment of metastatic cancer patients. Various investigators have already identified specific cell types from TME that are involved in the progression and resistance of cancer cells[2]. These include circulating tumour cells (CTCs), cancer-associated fibroblasts (CAFs), cancer stem cells (CSCs), immune cells, endothelial cells, etc., from highly metastatic cancer patients. The development of this support niche is critical for persistent uncontrolled growth of cancer at the metastatic stage. This special issue on "Tumour Microenvironment in Therapy of Metastatic Cancer" describes various cell types and components involved in tumour growth, invasion and metastasis, and also addresses various strategies that can be implemented to target these resistant cancer cells for effective cure of metastatic cancer in the near future.

Keywords: Tumour Microenvironment; Invasion; Metastasis; Extracellular Metrix; Immune Cells; Cancer.

This special issue has an interesting review written by Dr. Autokick Singh from the Department of Genomic Medicine at MD Anderson Cancer Centre, Houston Texas, USA with their working group in India (Anjali Bhargav et al. 2023) on the role of various immune cells and their interaction in the TME for promotion, progression, invasion, and metastasis. The authors have stated that the TME mainly harbours adaptive and innate immune cells, which include T and B lymphocytes, natural killer (NK) cells, macrophages, neutrophils, and dendritic cells[3]. These cells probably help in promoting and supporting tumour growth and invasion. Dr. Singh and his group have highlighted various factors that help immune cells during angiogenesis and metastasis. They have also shown that the elevation of CAFs and degradation of extracellular matrix (ECM) by proteolytic enzymes aid in cancer progression resulting in uncontrolled cell proliferation, increasing oxygen demand in the blood vessels and creating hypoxic conditions in TME. Thus, the hypoxia in TME can lead to alterations in gene expression to increase autophagy and inhibit apoptosis. Tumour-infiltrating lymphocytes (TILs) in TME may represent a prognostic indicator for immunosuppression, but further studies are required to understand the underlying mechanism. This may provide a better opportunity to translate a basic understanding of various components of TME into therapeutic advancements. Thus, understanding the exact role of immune cell types in the TME may help in designing appropriate molecular targeted therapies for effective cure of metastatic cancer.

Another interesting review on "Tumour Microenvironment and associated cell types involved in metastatic cancer" written by Srirupa G. Choudhari and Potdar from the Department of Biotechnology, Pondicherry Central University, Puducherry, India clearly mentions that the TME is highly dynamic and plays an important role in cancer development, progression, invasion, and dissemination. Various cellular components like immune cells, blood vessels and stromal cells, and non-cellular components comprising ECM and exosomes are involved in the metastatic process of cancer[2]. The authors have further stated that different types of metastatic cancers possess distinct phenotypes of TME, which should be considered while designing individualized cancer therapy for different patients. Thus, this review mainly emphasizes on different roles of individual cell types involved in the TME in the progression and promotion of metastasis of tumour cells. The authors have further suggested that the targeting of all these cell types in the TME may lead to better cancer therapies in the future.

Monitoring metastatic cancer therapy is often difficult due to the non-availability of tissue biopsy, which is one of the major reasons for the high mortality rate of metastatic cancer patients

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worldwide. However, in the last decade, a non-invasive biopsy called "liquid biopsy" has been established, which is a fast, non-invasive, and more sensitive method for cancer diagnosis and therapy[4]. Omkar Khade and his group from the Indian Institute of Bioinformatics Bangalore, India have written a concise review on "Liquid Biopsies: As an Emerging Tool in Cancer Diagnosis and Therapy in Metastatic Cancer". Khade et al. have stated that liquid biopsies can be used for early diagnosis and real-time monitoring of tumour progression during cancer chemotherapy and targeted therapy. Various components and cell types in liquid biopsy are involved in the metastatic process such as CTCs, circulating DNA (ctDNA), circulating cell-free DNA (cfDNA), exosomes, microRNA (miRNA), tumour-educated platelets (TEPs), etc. The molecular profiling of all these components by next-generation sequencing (NGS) will help clinicians to know the exact phenotypes of the tumour cells for administering precise molecular targeted therapy. The expression of these biomarkers indicates a specific stage of metastatic cancer. Thus, liquid biopsy opens up a new avenue in the field of precision medicine. This review summarizes in-depth information on liquid biopsies, its various components, and their specific roles in monitoring metastatic cancer therapy.

Cancer is one of the most devastating diseases that poses a significant threat worldwide, mainly due to several unknown factors. Therefore, the diagnosis and therapies of cancers require further study. We have discussed above about the liquid biopsy and its components in the diagnosis and therapies of metastatic cancer. In a similar line of work, Manasi Gupta from the Biotechnology Department, Maharshi Dayanand University, Rohtak, India, and Pravin Potdar have written a brief review on the technology of liquid biopsy containing ctDNA analysis for evaluation and management of metastatic cancer. This review describes the role of ctDNA analysis in the diagnosis and therapy of metastatic cancer. Since a single tissue biopsy sample cannot represent the heterogeneity of the tumour cells, cancer research has now focused on the analysis of liquid biopsy containing ctDNA, where there are no limitations in repeated sampling during cancer treatment and it matches well with the genetic makeup of individual patients to determine the metastatic potency of this tumour[5]. Gupta and Potdar have explained ctDNA analysis and provided in-depth knowledge about the molecular profiling and biological characteristics of several tumour cell types, which is the most important technological development in ctDNA analysis for monitoring therapy of metastatic cancer. Liquid biopsy containing ctDNA analysis is an advanced technique to identify gene mutations in specific tissue types with 70−75% accuracy. Gupta and Potdar have also explained the technological protocols used for the analysis of ctDNA which include the most sensitive and specific profiling by NGS, simple polymerase chain reaction (PCR) technology and deep sequencing PCR. They have further stated that the analysis of ctDNA can be enhanced using these methods to obtain more accurate results. Thus, this review has explained the in-depth technological analysis of ctDNA for diagnosis and therapy of metastatic cancer for better cure.

The latest epidemiological survey has shown that the mortality rate is more than 50% despite the availability of various innovative cancer therapies. Thus, there is a need for specific therapy that can kill cancer cells without harming normal cells. Immunotherapy is one of the latest innovations in cancer treatment, which includes immune checkpoint inhibitors (ICI), adoptive cellular therapies, cancer vaccines, and chimeric antigen receptor (CAR) T-cell therapy. CAR T-cell therapy has shown great promise in curing lymphomas and myelomas, without major toxic effects[6]. Six such therapies are now approved by the US FDA for haematological malignancies. This therapy involves the bioengineering of a cancer patient's T-cells with CAR in the lab so that they can specifically attack cancer cells without harming normal cells. Ankita Singh from the Department of Microbiology, the University of Delhi South Campus, New Delhi, India along with Dr. Pravin Potdar have written a descriptive review on "Updating CAR-T Cell Immunotherapy for Liquid and Solid Tumour" where they have highlighted this therapy for lymphomas and myelomas, along with a few trials on solid tumours. However, they have mentioned certain limitations of CAR T-cell efficacy due to the heterogeneity of solid tumours. Singh and Potdar have further stated that CAR T-cell therapy is groundbreaking, as it leads to effective and long-lasting therapeutic outcomes. There are two ways to prepare CAR T-cells: one is from the patient's T cells called autologous CAR T-cells, and the other is from a donor's T cells called allogeneic CAR T-cells. The authors have explained the design of CAR for this therapy along with the protocol to produce CAR T-cells and then administer these cells into the patient's body as a treatment to cure cancer. They have also discussed the various viral and non-viral vectors used for making CAR T-cells. Singh and Potdar have cited various ongoing clinical trials using CAR T-cells for the therapy of metastatic cancer. They have also mentioned the latest automated system "CliniMACS Prodigy System" to expedite the production of CAR T-cells. Thus, to improve the specificity and efficacy of CAR T-cell therapy, many approaches are being used to achieve precise immunotherapy to cure haematological malignancies and solid tumours. This review covers the most recent advancements and enhancements in CAR T-cell therapies for lymphomas and solid tumours as well as methods to overcome their drawbacks.

Heat Shock Protein 72 (HSP 72) is overexpressed in various human cancers and plays an important role in tumour cell proliferation, invasion, and metastasis[7]. These proteins are exported into the TME and modulate the immune response against cancer cells. In this special issue on TME, Muneera Sahib and Marsico from Chester Centre for Stress Research, Chester Medical School, University of Chester, United Kingdom have contributed their original work on "Anti-Cancer Agents Work in Antagonism with Inhibitors of HSP 72". They have used acute myeloid leukaemia (AML) cell line U937 and chronic myeloid leukaemia (CML) cell line K562 to evaluate the effect of Pifithrin chloride (PES-Cl), an inhibitor of HSP 72 protein activity, as a single agent or in combination with chemotherapeutic agent Bortezomib in order to elucidate the activity of these agents in cellular apoptosis. They are the first to investigate the potential activity of PES-Cl as an HSP 72 inhibitor in combination with Bortezomib in leukaemias. Their overall data confirmed the complexity of the proteostasis network in cancer cells and concluded that special attention is required in the selection of HSP inhibitors in combination with chemotherapeutics to achieve better treatment in respective cancers. However, they have stated a need for prospective studies to elucidate the mode of action of these agents, to potentially overcome resistance to canonical chemotherapy and improve the therapeutic potential of leukemia treatments.

We have received several interesting reviews and original articles from various authors worldwide for the special issue on "Tumour Microenvironment in Metastatic cancers". Most of these articles suggest a need for understanding the exact mechanism of cancer metastasis and more focus on various components of the TME, which are responsible for invasion and metastasis. It is critical to examine this process and target these cell types as well as the signalling pathways responsible for invasion and metastatic potential of tumour cells to achieve better therapies. I hope that this special issue will provide valuable information to cancer researchers, clinicians, and academicians to enhance their knowledge of the TME and its components to achieve better therapy for patients with metastatic cancers.

Abbreviations

AML, Acute Myeloid Leukaemia; CAFs, Cancer-Associated Fibroblasts; CAR, Chimeric Antigen Receptor; cfDNA, Circulating Cell-Free DNA; CML, Chronic Myeloid Leukaemia; CSCs, Cancer Stem Cells; CTCs, Circulating Tumour Cells; CtDNA, Circulating DNA; ECM, Extracellular Matrix; HSP 72, Heat Shock Protein 72; ICI, Immune Checkpoint Inhibitors; miRNA, microRNA; NGS, Next-Generation Sequencing; OS, Overall Survival; PCR, Polymerase Chain Reaction; PES-Cl, Pifithrin Chloride; TEPs, Tumour-Educated Platelets; TILs, Tumour-Infiltrating Lymphocytes; TME, Tumour Microenvironment.

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Conflicts of interest

The author declared that there are no conflicts of interest.

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