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Review Article

Tumor Micro environment

Understanding The Influence of Tumour Microenvironment Variability On Therapeutic Effectiveness

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Abstract: Cancer immunotherapy has proven effective in treating malignant diseases, but only a small percentage of patients experience complete and durable responses to current treatments. This highlights the need for more effective immunotherapies, combination treatments, and predictive biomarkers. The molecular properties of a tumor, intratumor heterogeneity, and the tumor immune microenvironment are key targets for precision cancer medicine. Humanized mice that support the engraftment of patient-derived tumors and recapitulate the human tumor immune microenvironment of patients represent a promising preclinical model for addressing fundamental questions in precision immuno-oncology and cancer immunotherapy. The microenvironmental physiology of tumors is unique from normal tissues, characterized by oxygen depletion, glucose and energy deprivation, high lactate levels, and extracellular acidosis. Hypoxia and other hostile microenvironmental parameters can confer resistance to irradiation, leading to treatment failure. Pretreatment assessment of critical microenvironmental parameters is needed to select patients who could benefit from special treatment approaches, such as hypoxia-targeting therapy. Acquired resistance to various therapeutic interventions is a hallmark of cancer, and the tumor microenvironment (TME) plays a crucial role in cancer progression, particularly therapeutic resistance. Targeting the TME as an essential strategy to overcome cancer resistance and improve therapeutic outcomes through precise intervention is highly desired. Cell stem cells (CSCs) play a pivotal role in tumorigenesis, tumor progression, and metastasis. The inflammatory microenvironment is an essential component of the tumor microenvironment, and understanding the key factors that exert important actions in the tumor process would be important to improve clinical outcomes.

Keywords: Tumour Vascularity; Tumour Hypoxia; pH in the tumour; Fibroblasts; Nanoparticle.

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1. INTRODUCTION

The physiological characteristics of tumors distinguish them significantly from normal tissues. The uniqueness of this condition is characterized by factors including oxygen depletion (hypoxia and anoxia), extracellular acidosis, increased lactate levels, restricted glucose supply, energy depletion, significant interstitial fluid dynamics, and heightened interstitial hypertension[1] . The competition conditions in the tumor microenvironment are primarily influenced by the abnormal tumor microcirculation. The tumor vasculature undergoes robust proliferation, resulting in the formation of immature, structurally defective, ineffective microvessels. As a result, tumor blood flow becomes disorderly and exhibits heterogeneity. The advancement of tumors encompasses the simultaneous expansion of both malignant cells and benign components within the surrounding stroma. The interactive relationship between pathologically altered parenchyma and stroma within the Tumor Microenvironment (TME) is currently acknowledged as a pivotal paradigm, deemed one of the characteristic hallmarks of cancer[2]. Among the various activities associated with TME, the clinical response to therapies stands out as a major determinant of the long-term prognosis for patients undergoing anticancer interventions. The progression of cancer occurs concurrently with the surrounding tumor microenvironment (TME), resulting in sustained proliferation and subsequent metastasis, a phenomenon intricately associated with the majority of fatalities attributed to cancer[3]. Despite notable advancements in therapeutic approaches, addressing disease relapse with constrained responsiveness poses a substantial challenge, thereby impacting the clinical prognosis in oncology. The tumor microenvironment (TME) assumes a crucial role in orchestrating innate resistance preceding cytotoxic treatment interventions, primarily through ongoing reciprocal interactions between cancer cells and adjacent TME elements[4]. This form of resistance is distinct from inherent resistance, which originates from the initial genomic and/or epigenomic alterations in cancer cells. The complex interaction among diverse elements in the microenvironment, notably immune cells, is unveiling novel targets for therapeutic intervention[5]. The evolving complexity and dynamic nature of the tumor microenvironment are revealing an intricate network involving diverse cell types, including infiltrating immune cells (such as T and B cells), mast cells, and antigen-presenting cells (such as macrophages and dendritic cells)[6.] This setting comprises numerous elements, such as cancer cells, stromal tissue consisting of immune cells, fibroblasts, myofibroblasts, cytokines, and vascular components, all intricately interwoven within the extracellular matrix that surrounds this intricate ecosystem. Within this setting, Cancer Stem Cells (CSCs) play a crucial role, acting as significant contributors to the maintenance of cancer heterogeneity and playing a role in the advancement of the disease. Cancer stem cells (CSCs) exhibit extraordinary capabilities that empower them to facilitate the sustained progression of cancer. Their ability to undergo self-renewal and differentiation forms the foundation of their involvement in preserving the varied cell populations within the tumor. Additionally, CSCs play a crucial role in the emergence of resistance mechanisms, a key factor in enabling cancer to endure therapeutic interventions. The resistance mechanisms utilized by CSCs involve a diverse array of strategies. These include the ability to decrease replication, posing a challenge to conventional therapies that aim at rapidly dividing cells. Moreover, CSCs can activate drug export systems, effectively expelling anti-cancer drugs and diminishing their efficacy, thereby playing a role in the development of treatment resistance. Additionally, CSCs participate in epithelial-to-mesenchymal transition (EMT), a phenomenon where cells shift from a relatively stationary and cohesive state to a more mobile and invasive one[7]. This shift is closely linked to metastasis and resistance to treatment. Furthermore, CSCs contribute to heightened resistance to hypoxia by promoting angiogenesis, ensuring an ample blood supply for the tumor. They contribute to immune evasion by reducing the expression of certain molecules and enhancing the production of anti-inflammatory cytokines and growth factors[8]. Understanding the varied functions of CSCs within the tumor microenvironment is essential for advancing the progress of more effective cancer therapies. Targeting these distinctive cells may be pivotal in enhancing the effectiveness of cancer treatments and ultimately mitigating the impact of cancer on human health[9].

2. VASCULARITY OF TUMOUR

The newly developed microvessels in most solid tumors demonstrate variations from the usual morphology observed in the vasculature of the surrounding tissue. These microvessels within solid tumors show significant structural and functional abnormalities, such as dilation, tortuosity, elongation, and sacculation. The development of the vascular network in tumors entails the creation of new blood vessels. This process includes co-opting and modifying pre-existing mature vessels or the differentiation of endothelial precursors derived from the bone marrow[10]. Each of these processes plays a role in the overall vascular development and contributes to the heterogeneity observed. The well-being of the vasculature plays a vital role in the survival and metastatic advancement of tumors by enabling the distribution of oxygen and nutrients. Nonetheless, inadequately structured tumor vasculatures may result in hypoxia and limitations in the delivery of growth factors, impeding proper growth. Excessive branching is often associated with the presence of blind vascular endings. In cases where the endothelial lining is insufficient or absent, and basement membranes are disrupted, there is an increase in vascular permeability. The extravasation of blood plasma and red blood cells occurs, causing an increase in hydrostatic pressure within the tumor interstitium and expansion of the interstitial fluid space (table 1). Tumor vessels display considerable spatial heterogeneity, and the microcirculation within a tumor shows notable temporal heterogeneity[11]. Together, these factors lead to a significantly anisotropic distribution of tumor tissue oxygenation and interconnected elements. The blood circulation within tumors varies significantly, ranging from 0.01 to 2.0 ml/g/min. Therefore, tumors may have flow rates similar to cells with high activity from metabolism or circulation rates similar to tissues with low metabolic turnover. The intricate interaction among various cell types in the Tumor Microenvironment (TME), including endothelial cells, pericytes, and bone marrow-derived precursor cells, is crucial in the tumor vascularization process[12]. The spatial separation between blood vessels and tumor focal points establishes an infiltration gradient, impacting the distribution of drugs to cancer cells in the tissue. Concurrently, microvessel density (MVD) emerges as a significant predictor of clinical outcomes in malignant

conditions. Mesenchymal stem cells (MSCs), tumor-associated macrophages (TAMs), and cancer-associated fibroblasts (CAFs) collectively contribute to tumor vascularization by releasing diverse angiogenesis-related ligands into the TME[13]. Notably, an increased expression of the pro-angiogenic factor Vascular Endothelial Growth Factor A (VEGFA) is closely linked to a poorer prognosis in metastatic colorectal, lung, and renal cell cancers[14].

Table 1: Significant structural and functional irregularities within tumor microvessels are addressed in this section.
Vascular system
Absence of Distinction
Disruption of vascular organization
Augmented gaps between vessels
Presence of non-vascular regions
Enlarged sinusoidal microvessels
Stretched, winding vessels
Shape irregularities
Pouch-like microvessels, dead ends
Abnormal branching patterns
Disrupted endothelial lining, fenestrae
Discontinuous or missing basal membranes
Absence of luminal endothelial cell cords
Presence of non-communicating vessel-like spaces
Presence of tumor cell-lined pseudo-vascular channels ("mimicked vasculature")
Arteriovenous connections (bypasses)
Vessels emerging from the venous side
Absent nerve supply
Deficiency in physiological/pharmacological receptors
Absence of smooth muscle components
Insufficient pericytes
Lack of vasomotion
Deficiency in flow regulation
Enhanced vascular permeability, plasma seepage
Elevated geometric resistance to flow
Increased viscous resistance to flow
Fluctuating flow velocities (in approximately 80% of all microvessels)
Unstable flow direction
Intermittent flow, backflow (in about 10% of all microvessels)
Flow stagnation (in about 2% of all microvessels)
Plasma perfusion exclusively
Clustering of platelets and leukocytes
Blood clot development
Agglomeration of red blood cells
Diminished Fahraeus-Lindqvist phenomenon
Lymphatics
Frequently invaded by tumor cells (peripheral vessels)
Vessels with flattened morphology and absent lumen (central vessels)
Tumor margin growth induced by VEGF-C
Insufficient lymphatic drainage within the tumor core
Flow of interstitial fluid
Elevated interstitial pressure

3. FLUID FLOW IN THE INTERSTITIAL SPACE

The growing tumor generates new microvessels, often with abnormal permeability, but lacks the ability to establish a functional lymphatic network. Consequently, a significant movement of unbound fluid occurs within the interstitial space due to substantial hydraulic conductivity. Unlike the convective currents observed in the interstitial compartment of normal tissue, which make up about 0.5% to 1% of plasma flow, human cancers demonstrate interstitial water flux levels that can reach up to 15% of the corresponding plasma flow (fig 1)[15]. Upon extensive infiltration of the tumor's microvessels, there is a substantial accumulation of fluid within the tumor matrix, leading to increased interstitial pressure within solid tumors. In contrast to the slightly subatmospheric or marginally above atmospheric interstitial fluid pressure found in normal tissues, cancers exhibit interstitial hypertension, with mean values exceeding 15 mm Hg and extending beyond. This heightened interstitial fluid pressure causes the outward movement of fluid from areas of high pressure to those with lower pressure at the boundary between the tumor and normal tissue[16].

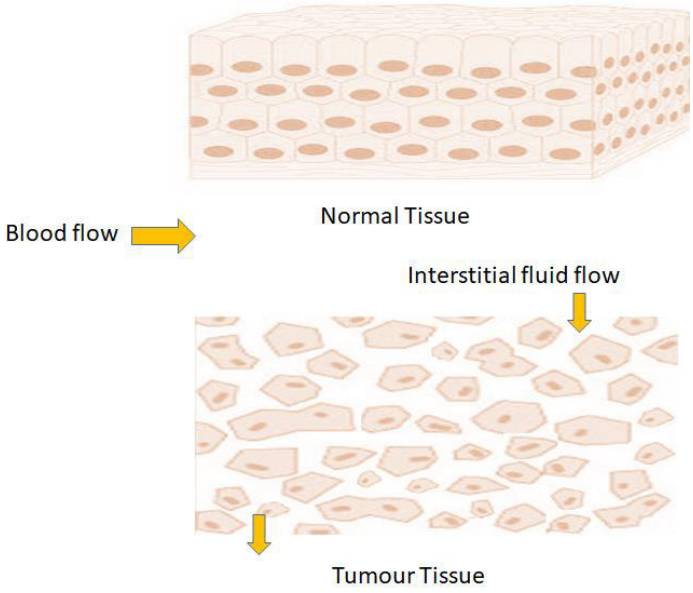
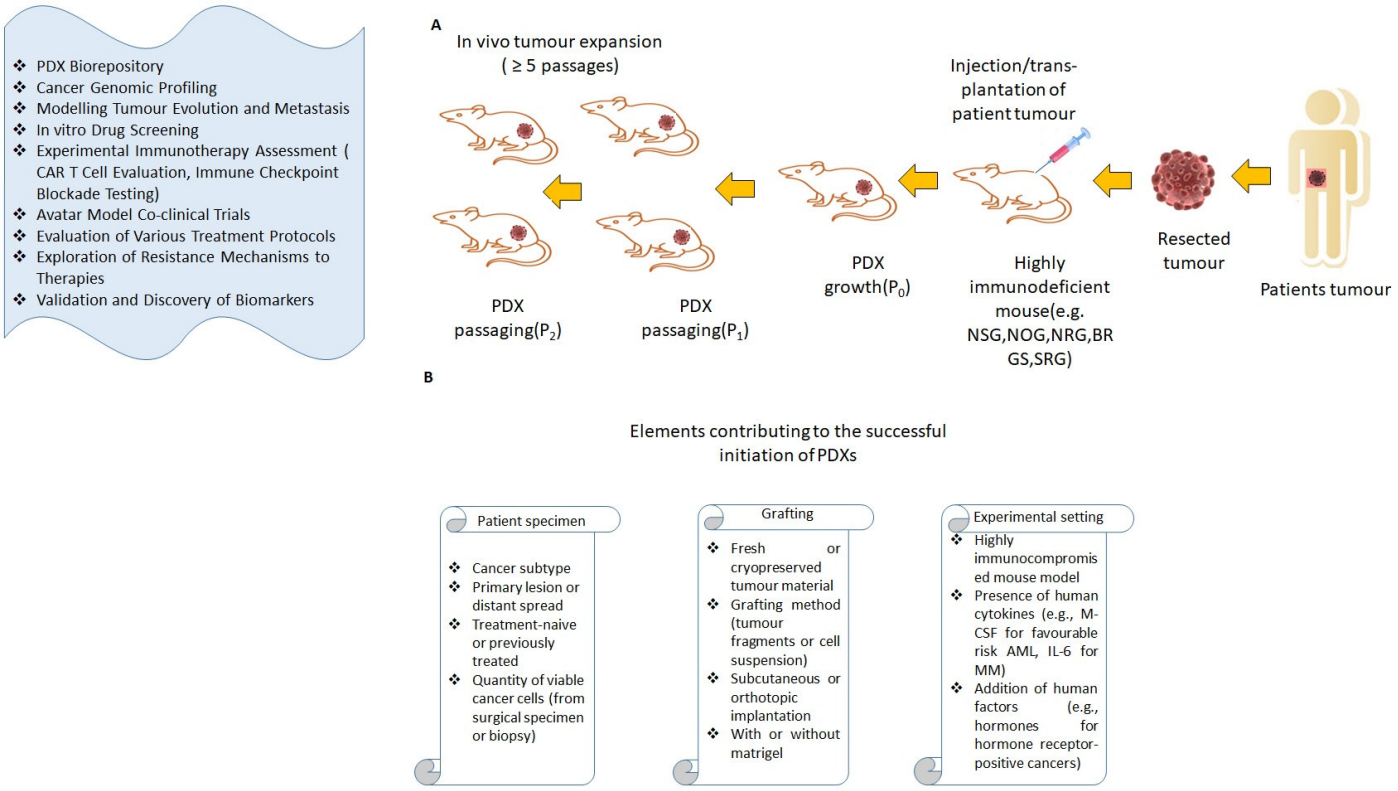


Fig 1: Interstitial fluid flow (IFF) in relation to blood flow (TBF) is depicted through a schematic representation illustrating convective fluid currents in both normal and tumor tissues in the upper section.

4. MODEL OF TUMOUR MICRO ENVIRONMENT

A significant impediment within the field of oncology lies in the challenge of translating findings from preclinical models to clinical applications. The overwhelming reality is that over 95% of anticancer drugs, which demonstrate efficacy in preclinical studies, ultimately prove ineffective during clinical trials. Addressing this issue and improving the evaluation of innovative immunotherapies, along with identifying optimal combinations of anticancer drugs, has led to the development of sophisticated mouse models, commonly referred to as "humanized mouse models"[17]. These models facilitate the growth of tumors obtained from patients and the establishment of a functional human immune system. While cancer immunotherapy has demonstrated significant clinical benefits in numerous individuals with malignant diseases, the existing range of immunotherapies delivers comprehensive and sustained responses in only a specific subset of patients. Highlighting the critical need for advanced immunotherapies, combined treatments, and predictive biomarkers, the molecular attributes of tumors, intratumor heterogeneity, and the tumor immune microenvironment emerge as crucial factors influencing tumor evolution, metastasis, and resistance to therapy[18] . Consequently, these elements become of utmost significance in the field of precision cancer medicine. Robust models in the realm of human biology, diseases, and therapeutic interventions are exemplified by humanized mice, which are either characterized by xenografting with human cells or by genetic modification to express human genes. Humanized mouse models play a pivotal role in accurately reproducing essential aspects of human biology and pathology, serving as a foundational cornerstone for translational biomedical research and the development of strategies in precision medicine. The advancement of next-generation humanized mouse models, utilizing patient-derived tumor xenografts (PDX), presents significant promise for assessing the preclinical efficacy of combined (immuno)therapies and treatment protocols[19] . These models enable the discovery of treatment responsiveness biomarkers and the categorization of cancer patients for potential inclusion in clinical trials. In comparison, cell line-derived xenograft (CDX) models, employing in vitro immortalized tumor cells derived from patient tissues, have become a widespread tool in the field of preclinical drug development. Although CDX models have been widely embraced, they often struggle to accurately capture tumor heterogeneity and demonstrate limited predictive effectiveness in phase III clinical trials. This deficiency plays a substantial role in the high attrition rates observed in drug development within the cancer research domain[20]. The establishment of cancer cell lines presents a notable challenge, particularly evident in colorectal cancer (CRC) and pancreatic cancer, where success rates are approximately 10%[21,22]. As a result, the field of oncology faces constraints, relying on a limited number of human CDXs for each cancer type to conduct preclinical assessments of anticancer drugs. The process of creating patient-derived xenografts (PDXs) involves implanting patient tumours, either in the form of a single-cell suspension or tissue fragment, into immunodeficient mice. These mice undergo continuous in vivo propagation for at least 3–5 passages. PDX models are highly regarded for their ability to faithfully replicate histological features, molecular characteristics, and intratumor heterogeneity observed in human cancers. This replication allows them to overcome specific limitations associated with CDX models[23]. While PDX models are valuable, their use faces challenges in thoroughly studying the interaction between human tumor cells and the human immune system. This limitation hinders a comprehensive evaluation of the effectiveness of cancer therapies targeting immune cells. To address this issue, humanized PDX mouse models, which incorporate a human immune system, have been introduced in response to this challenge. These innovative models showcase significant potential as an in vivo platform for advancing translational research in immuno-oncology. They serve as a valuable tool for investigating cancer immunotherapies, exploring tumor immune evasion, and examining the role of immune cells in tumor progression and metastasis, as detailed in the provided source[24]. At present, there are around 1500 active clinical trials dedicated to assessing a variety of cancer immunotherapies. These

include immune checkpoint inhibitors (ICIs), antibody-based treatments, immunomodulatory drugs, cytokines, CAR cells, therapeutic cancer vaccines, and oncolytic viruses. These trials are meticulously documented on ClinicalTrials.gov. Elaborately crafted mouse models with advanced humanization features aim to enhance both adaptive and innate immune systems. Furthermore, these models are designed to streamline the creation of Patient-Derived Xenografts (PDXs) from a diverse range of cancer types. This collaborative initiative is positioned to accelerate preclinical evaluations of innovative immunotherapies, facilitating the identification of biomarkers and the development of effective treatment protocols and combination therapies[25].



Creating models of tumors derived from patients involves implanting patient tumors into immunodeficient mice.

A) These models, known as Patient-Derived Tumor Xenografts (PDX), undergo in vivo expansion through successive passages, contributing to the establishment of a PDX biobank.

B) The success of PDX establishment is influenced by factors such as the initial growth and in vivo propagation for a minimum of 5 passages.

5. HYPOXIA IN THE TUMOUR MICROENVIRONMENT

The presence of hypoxic tissue zones, characterized by reduced oxygen tensions (pO2 values falling below 3.5 mm Hg), represents a significant pathophysiological feature observed in locally advanced solid tumors. This occurrence is observable in a range of human malignancies, including cancers that impact different anatomical locations such as the breast, uterine cervix, vulva, head and neck, prostate, rectum, pancreas, brain, soft-tissue sarcomas, and malignant melanomas[26] . A substantial percentage, ranging from 50% to 60%, of solid tumors at an advanced local stage exhibit heterogeneously distributed regions featuring low oxygen levels, commonly referred to as within the tumor bulk, there are hypoxic and/or anoxic zones. The presence of hypoxic (or anoxic) zones arises due to an oxygen supply and consumption imbalance. Unlike regular tissues or organs, where oxygen supply aligns with metabolic requirements, locally advanced solid tumors experience a heightened oxygen consumption rate by neoplastic (as well as stromal) cells, exceeding the available oxygen supply. This mismatch leads to the formation of tissue regions marked by significantly diminished oxygen levels. The manifestation of hypoxia in solid tumors involves significant pathogenetic mechanisms, including notable structural and functional irregularities in the tumor microvessels, causing restricted oxygen delivery due to impaired perfusion[27] . Furthermore, the degradation of diffusion geometry contributes to restricting oxygen delivery, resulting in diffusion-limited oxygen transport. Tumor-associated or therapy-induced anemia reduces the blood's ability to transport oxygen, resulting in anemic hypoxia. Additionally, an increase in diffusion distances causes cells located far from nourishing blood vessels to receive inadequate oxygen and nutrients. This situation, known as diffusion-limited hypoxia or "chronic" hypoxia, worsens in the presence of tumor-related or therapy-induced anemia[28] . The role of anemic hypoxia becomes particularly prominent, accentuated in tumor regions with diminished perfusion rates. Tumor microvessels frequently rely on plasma for perfusion, albeit transiently. As a result, a rapid development of hypoxia occurs in the vicinity of these vessels. Only a restricted set of tumor cells at the arterial end can acquire an adequate oxygen supply under the existing conditions, referred to as hypoxemic hypoxia. While physiological compensation by normal tissues can mitigate

oxygen deficiency, locally advanced tumors or extensive tumor regions encounter difficulties overcoming constraints on oxygen supply, resulting in the initiation and progression of hypoxia. Cells exposed to low oxygen levels demonstrate a reaction characterized by a decrease in overall protein synthesis, resulting in restricted proliferation and eventual cell death[29] . Ample evidence suggests that low oxygen levels can hinder or completely halt the proliferation of (tumor) cells in a laboratory setting. Extended exposure to low oxygen conditions can bring about changes in the distribution of the cell cycle and the prevalence of quiescent cells, subsequently impacting the response to radiation. The degree of inhibition depends on the severity and duration of low oxygen levels, along with the concurrent presence of other environmental deficiencies. The levels of low oxygen needed to cause a disproportionate elongation of the G1 phase or an accumulation of cells in this phase range from 0.2 to 1 mm Hg. Beyond this "low oxygen threshold," the environmental oxygen status appears to have minimal effects on the proliferation rate[30] .

6. EXTRACELLULAR MATRIX

The fibrous network intricately formed by the extracellular matrix (ECM), which originates from diverse cell types within the tumor microenvironment (TME), serves a role that extends beyond providing structural support, encompassing the regulation of various cellular activities[31] . Significantly, the extracellular matrix (ECM) associated with the tumor microenvironment (TME) diverges notably from the ECM present in healthy tissue. It serves as a fundamental scaffold, enabling the invasion of cancer cells via chemotaxis[32] . The Extracellular Matrix (ECM), which is made up of collagen, elastin, proteoglycans, and specific structural proteins, helps to maintain cell integrity and division inside host tissue. Various cells, notably fibroblasts, contribute to synthesizing these ECM components. Matrix metalloproteinases (MMPs), possessing the ability to enzymatically break down protein macromolecules, contribute to the restructuring of the extracellular matrix (ECM)[33] . Acknowledged for their pro-angiogenic and metastatic characteristics, MMPs, particularly in breast cancer, significantly contribute to the promotion of tumor proliferation and invasion, playing a pivotal role in these processes. The phenomenon takes place as a result of extracellular matrix (ECM) digestion, facilitating the infiltration of cancer cells into both the host tissue and basement membrane. In the realm of breast cancer, the adherence of malignant cells to the ECM triggers changes in their polarization, resulting in resistance to apoptosis induced by etoposide[34] . Cell adhesion-mediated drug resistance (CAM-DR) is reliant on the interaction between integrin and components of the extracellular matrix (ECM), including fibronectin, collagen, and laminin[35] . In cancer progression through integrin signalling, the accelerated biosynthesis of ECM and increased crosslinking of collagen fibers in the reactive stroma play a pivotal role. Patients, especially those with breast neoplasia, can be categorized into specific groups, enabling prognostic predictions based on ECM composition and leading to diverse clinical outcomes[36] .Tumors with heightened expression of protease inhibitors in the ECM are associated with a favorable prognosis, while those with elevated levels of integrins and matrix metallopeptidases (MMPs) indicate an unfavorable prognosis, suggesting a potential for recurrence. Therefore, targeting therapeutic interventions toward the ECM, closely associated and functionally linked to tumors, could present an additional approach for treatment.

7. IMMUNITY RESPONSE

Under typical physiological circumstances, a proficient immune system efficiently coordinates robust anti-tumor reactions. Nonetheless, in pathological scenarios, immune suppression mechanisms may hinder this response, consequently promoting disease progression. In the realm of the tumor microenvironment (TME), the initiation of cytotoxic T cell activation transpires via extended interaction with inhibitory cell surface receptors. Instances of these receptors include cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and the programmed death 1 (PD-1) receptor, both vulnerable to ligand overexpression[37] . Myeloid-derived suppressor cells (MDSCs) play a crucial role in facilitating tumor progression by inhibiting T cell immunity, thereby supporting the growth, movement, and infiltration of malignant cells[38] . This collective effect contributes to the development of tumor resistance. The variability, flexibility, and susceptibility of myeloid-derived suppressor cells (MDSCs) pose challenges for therapeutic strategies, hindering effective targeting due to their responsiveness to numerous chemotherapeutic drugs. Studies indicate that tumor-infiltrating myeloid-derived suppressor cells (MDSCs) exhibit increased absorption of fatty acids and enhanced activation of fatty acid oxidation (FAO)[39]. The immunosuppressive characteristics inherent in the tumor microenvironment (TME) pose a substantial obstacle to the effectiveness of various cancer therapies that depend on the activation of immune cells against cancer. This constraint arises from tumors' adeptness at evading immune detection and destruction through various mechanistic levels. Macrophages, pivotal bone marrow-derived cells, play a central role in fostering tumor progression by promoting angiogenesis, invasion, and metastasis in vivo. Effective activation of naïve T cells against tumor antigens requires supplementary co-stimulatory signals, which are attained by engaging CD28 on the T-cell surface membrane[40] . The impressive advancements in cancer immunotherapy through immune checkpoint blockade have spurred extensive exploration and the development of alternative checkpoint inhibition strategies. Nevertheless, despite successful T cell infiltration towards cancer cells, the tumor microenvironment (TME) poses additional challenges that hinder their viability and functionality. Predominantly, cancers can impose metabolic constraints on T cells[41] .

8. EXOSOMES

Exosomes exhibit a distinctive cellular organization and house a significant collection of bioactive elements. They stem from large multivesicular bodies (MVBs) and are released into the extracellular environment through the fusion of MVBs with the plasma membrane[42] . Within the tumor microenvironment (TME), diverse cell types release exosomes, distributing them in bodily fluids like Blood, urine, saliva, ascitic fluid, and amniotic fluid are all examples of bodily fluids[43] . Research findings indicate that exosomes discharged by melanoma significantly contribute to the enhancement of both primary tumor expansion and metastasis. Moreover, these exosomes play a pivotal role in prompting the differentiation of (BMDCs) into a pro-metastatic phenotype through MET-mediated signaling.

Notably, the impact of these processes is significantly attenuated by inhibiting exosome function, as demonstrated in previous studies[44] . Exosomes originating from cancer cells have the capacity to sequester therapeutic antibodies, including rituximab and trastuzumab, thereby compromising the efficacy of immunotherapy[45] . Moreover, research indicates that exosomes released by fibroblasts can enhance the protrusion and motility of breast cancer cells. This effect is mediated by Wnt-planar cell polarity (PCP) signalling. This co-implantation of cancer cells alongside fibroblasts has unveiled pivotal insights into metastatic mechanisms. Research has illuminated a significant correlation between this co-presence and the activation of Planar Cell Polarity (PCP) activities[46] . Notably, the expression of CD81 within exosomes originating from fibroblasts has been identified as a crucial factor in this phenomenon. These findings underscore the intricate interplay between cellular elements within the tumor microenvironment, shedding light on the role of PCP signaling and exosomal CD81 expression in fostering metastasis. Understanding these connections holds promise for devising targeted interventions to impede metastatic progression and improve therapeutic strategies

9. INFLAMMATORY CELLS IN TME

In the intricate landscape of cancer development, inflammation emerges as a crucial player, amplifying signals that drive cell proliferation and survival, while also triggering invasion and metastasis. Interferons (IFNs), a versatile group of cytokines, participate in a range of biological functions, encompassing antiviral defense, cellular proliferation regulation, and modulation of immune responses. As a result, interferons (IFNs) play a complex role in tumor immunology, resembling a 'double-edged sword.'[47] Mesenchymal stem cells (MSCs), known for their versatile stromal properties and the ability to transform into diverse cell types like osteoblasts, chondrocytes, myocytes, and adipocytes, demonstrate both self-renewal and pluripotent differentiation capabilities[48] . IFNs establish intricate connections with cancer stem cells (CSCs), exerting influence on critical aspects including tumor cell proliferation, resistance to therapy, and the initiation of metastasis. Substantiating this established correlation, Schürch et al. presented evidence demonstrating that IFNs stimulate both the proliferation and differentiation of stem cells in chronic myeloid leukemia. Moreover, myeloid-derived suppressor cells (MDSCs), encompassing a diverse population that includes macrophages, dendritic cells, and granulocytes, play a pivotal role in modulating immune responses. Derived from the myeloid lineage, these immune cells consist of progenitors and precursors originating from bone marrow stem cells. Under normal physiological circumstances, immature myeloid cells (IMCs) undergo swift differentiation into mature granulocytes, macrophages, or dendritic cells. However, in pathological conditions such as cancer, infectious diseases, trauma, or specific autoimmune disorders, IMCs exhibit an aberrant differentiation process, resulting in the formation of myeloid-derived suppressor cells (MDSCs)[49] . The immune system experiences suppression due to various immunosuppressive factors emanating from myeloid-derived suppressor cells (MDSCs). More precisely, MDSCs stimulate the expression of miRNA101 in cancer cells, leading to the suppression of the corepressor gene C-terminal binding protein-2 (CtBP2). Subsequently, CtBP2 directly impacts crucial genes associated with stem cells, promoting cancer cell stemness and increasing metastatic and tumorigenic potential[50] . In the microenvironment of a tumor, tumor-associated macrophages (TAMs) represent a major immune cell group that infiltrates the tumor tissue. Although there was an initial belief that TAMs identified and eliminated tumor cells using different cytokines, recent studies have reached a consensus that TAMs actually play a vital role in fostering the growth, invasion, and migration of tumors[51] .

10. PH IN THE TUMOUR MICROENVIRONMENT

Maintaining a neutral to alkaline intracellular pH (pH_i) is a characteristic feature of tumor cells, contingent upon the absence of oxygen and energy deprivation[52] . Tumor cells utilize efficient mechanisms to extrude protons into the extracellular space, leading to the formation of an acidic microenvironment within tumors. Consequently, this results in the establishment of a pH gradient across the cell membrane, where the intracellular pH exceeds the extracellular pH, a pattern that contrasts with the typical state observed in normal tissues[53] . The acidification of tumors primarily stems from the increased transformation of glucose into lactic acid by cancer cells, coupled with metabolic acidosis. This process leads to the accumulation of protons and an elevation in respiratory quotients. Importantly, the upregulation of carbonic anhydrase (CA) induced by hypoxia emerges as a vital physiological adaptation[54] . This adaptation is remarkable as the cumulative carbon dioxide (CO2) emission exceeds the CO2 produced through substrate oxidation, leading to a notable elevation in the respiratory quotient beyond a pH level of 1.5. Such a shift underscores an intriguing metabolic transition, suggesting an augmented reliance on alternative pathways or non-oxidative metabolic routes[55]. This deviation from conventional respiratory patterns indicates a substantial metabolic reconfiguration, possibly reflecting an adaptive response to environmental or physiological stimuli. Understanding this divergence may offer insights into nuanced metabolic pathways and their potential implications in diverse biological contexts, shedding light on cellular adaptations under varying conditions.

11. LACTATE ACCUMULATION IN THE TUMOUR MICROENVIRONMENT

The accumulation of lactate serves as a discerning indicator signifying the malignant potential in squamous cell carcinomas that impact the uterine cervix, head, and neck, as well as colorectal adenocarcinomas. Noteworthy is the observation that concentrations of lactate in viable tumor regions display significant variations both within and between tumors, unlike levels of glucose and adenosine triphosphate[56] . Interestingly, a negative correlation is apparent between tumor glucose levels and lactate concentrations. This acidic milieu not only fosters tumor proliferation but also modulates the tumor microenvironment, influencing therapeutic response. Lactate accumulation contributes to immune suppression, impeding drug delivery and promoting resistance mechanisms[57]. Understanding the intricate interplay between lactate, metabolic dysregulation, and treatment outcomes unveils potential targets for therapeutic intervention. Strategies targeting lactate transporters or metabolic pathways may mitigate the hostile tumor microenvironment, enhancing treatment efficacy. Moreover, innovative approaches focusing

on metabolic reprogramming could revolutionize cancer therapies. Deciphering lactate's multifaceted role holds promise in refining treatments, aiming for improved responses in diverse solid tumor settings. These parameters, along with undisclosed factors, may play a direct or indirect role in the progression of tumors and the development of resistance to treatment.

12. MICROENVIRONMENT INFLUENCING RADIOTHERAPY RESISTANCE

The Primary Source of Radiation-Induced Cytotoxicity Lies in Genomic DNA Damage, Leading to Cellular Death. Radiation's Impact on Cellular Atoms and Molecules Generates Highly Reactive Free Radicals, Indirectly Influencing Genomic DNA and Irreversibly Culminating in Cell Death, Especially in the Presence of Oxygen. Extensive Research Focuses on Tumor Hypoxia and Angiogenesis to Improve Radiation Therapy's Effectiveness by Addressing the Unique Microenvironment of Malignant Solid Tumors, Distinguished by Variances in pH, Nutrient Distribution, Oxygen Levels, and Other Factors[58] . In oxygen-rich environments, molecular oxygen plays a key role in catalyzing the oxidation of DNA radicals, resulting in the formation of irreversible DNA damage. On the flip side, when exposed to hypoxic conditions marked by an oxygen depletion, the primary disturbance stems from the reduced production of reactive and cytotoxic species induced by ionizing radiation. The lack of oxygen lessens the severity of irreparable DNA double-strand breaks (DSBs), thereby contributing to the radioresistance of cells in hypoxic environments. The growth of solid tumors requires angiogenesis to reach a diameter of 2 mm, ensuring the acquisition of essential oxygen and nutrients. The angiogenic switch represents a crucial phase in tumor development, transforming an initially avascular tumor nodule into a rapidly expanding, highly vascularized tumor. Despite predictions of increased tumor hypoxia with antiangiogenic therapy, preclinical studies consistently show synergistic effects when combining radiation therapy with antiangiogenic agents, as observed with angiostatin[59] . Various strategies have been devised to counteract radioresistance associated with hypoxia, including methods to enhance oxygen delivery, the development of radiosensitizers tailored for hypoxic tumor cells, hypoxic cytotoxins, and inhibitors targeting hypoxia-inducible factor-1 (HIF-1). Examples of interventions include hyperbaric oxygen therapy, carbogen combined with nicotinamide, blood transfusion, and erythropoietin. Hyperbaric oxygen (HBO) therapy entails inhaling 100% oxygen at elevated pressure, offering a promising approach to alleviate tumor hypoxia by dissolving oxygen in the plasma and transporting it to tumor sites independently of haemoglobin[60] . Concurrently, the strategy aims to increase oxygen levels within the tumor region. Carbogen, a gas mixture of oxygen (O2) and carbon dioxide (CO2), is known for its effectiveness in alleviating diffusion-limited hypoxia when inhaled. Nicotinamide, the amide derivative of vitamin B6, acts as a vasoactive agent, relieving acute hypoxia. The administration of nicotinamide has been observed to alleviate perfusion-related acute hypoxia, potentially contributing to the rationale behind the observed radiosensitizing effect in combined therapy with carbogen. Furthermore, a correlation has been established between diminished hemoglobin levels and tumor hypoxia[61] .

13. OBESITY AND TUMOUR MICROENVIRONMENT

The prevalent description of obesity revolves around an elevated body mass index (BMI), mainly resulting from an excess accumulation of adipose tissue. Adipose tissue, functioning as a dynamic endocrine organ crucial for maintaining energy balance, becomes particularly noteworthy in this context. Uncontrolled hyperadiposity often leads to metabolic imbalances, disruptions in steroid hormone synthesis, and persistent subclinical inflammation[62] . These physiological consequences have been linked to the initiation and progression of tumors[63] . Various cancers associated with obesity, including those affecting the breast and visceral organs, emerge either within or in close proximity to adipose deposits. This implies that changes in adipose biology, commonly observed in elevated BMI scenarios, locally promote different types of cancer. Prolonged tissue damage, such as inflammation in adipose tissue, can trigger similar wound healing mechanisms, establishing a pro-neoplastic microenvironment. In individuals with obesity, white adipose tissue (WAT) is infiltrated by immune cells like macrophages and lymphocytes. Consequently, the obese fat pad resembles chronically injured tissue, serving as a potent source of proinflammatory mediators that may foster tumor growth. Moreover, when adipose tissue surpasses its blood supply, leading to hypoxia, adipocyte stress and subsequent cell death may occur[64] . In the context of hormone receptor-positive breast cancer, there is well-substantiated evidence indicating a correlation between inflammation in obesity-associated white adipose tissue (WAT) and mechanical changes in the extracellular matrix (ECM), thereby facilitating tumor growth[65] . The collective body of knowledge connecting adipose inflammation to a pro-tumor environment, both locally within the microenvironment and in the peripheral circulation, emphasizes the need for interventions focused on alleviating adipose inflammation as an innovative strategy for cancer prevention and treatment. The reduction of weight achieved through dietary modifications and/or exercise emerges as a compelling approach to correct dysregulated pathways in the obese state, holding considerable promise for both cancer prevention and treatment[66] .

14. FIBROBLASTS OF CANCER MICROENVIRONMENT

In the realm of solid tissues, fibroblasts play a crucial role in establishing the structural framework and maintaining physiological balance as a predominant mesenchymal lineage. Nonetheless, cancer-associated fibroblasts (CAFs) demonstrate functional differences from their normal counterparts, often carrying pathological implications. The conversion of normal fibroblasts into CAFs in the microenvironment is triggered by locally derived proteins such as fibroblast growth factor (FGF), monocyte chemotactic protein 1 (MCP-1), platelet-derived growth factor (PDGF), tissue inhibitor of metalloproteinase 1 (TIMP-1), and tumor-transforming growth factor ß (TGF-ß)[67] . Consequently, CAFs display aggressive proliferation, heightened extracellular matrix (ECM) deposition, and increased cytokine synthesis. Importantly, CAFs generate proinflammatory factors that drive tumor progression in an NF-κB-dependent manner, induce leukocyte infiltration, and enhance angiogenesis and vascular permeability[68] .

Establishing a synergistic partnership with cancer cells, cancer-associated fibroblasts (CAFs) play a pivotal role in fostering malignancy and imparting resistance to therapeutic interventions. In clinical contexts, traditional chemotherapy has been observed to induce phenotypic and metabolic transformations in stromal fibroblasts, leading to their conversion into CAFs. Stromal cells, particularly fibroblasts, release substances that induce paracrine or autocrine effects on tumor cells, leading to the initiation of a more aggressive cancer phenotype. In academic discourse, the activated fibroblasts that interact with tumor cells are commonly known as cancer-associated fibroblasts (CAFs)[69] . One crucial paracrine factor released by fibroblasts is hepatocyte growth factor (HGF), which binds to c-met receptors found on epithelial tumor cells. Consequently, cancer-activated fibroblasts can impact the progression of metastasis and tumor growth by releasing the chemoattractant HGF, potentially directing tumor cells to distant anatomical locations[70] .

15. NANOPARTICLE IN TUMOUR MICROENVIRONMENT

When administered systematically, nanoparticles encounter numerous physical, chemical, and physiological challenges as they strive to penetrate tumors and interact effectively with cancer cells. On a systemic level, circulating nanoparticles face the hurdle of uptake by reticulo-endothelial system (RES) organs, particularly the liver and spleen, resulting in significant sequestration before reaching the vascular compartment of the tumor. Exploring mild hyperthermia has emerged as a promising strategy to enhance nanoparticle uptake by tumors and bolster the treatment response [71]. Various methodologies can be simultaneously employed to induce hyperthermia and enhance chemotherapy drug delivery. These approaches include the concurrent application of external energy sources with pre-injected photothermal agents or intrinsically photothermal drug-carrying nanoparticles. Observations from hyperthermia treatment, as depicted in intravital microscopy images, reveal an increased liposome extravasation distance, leading to a twofold improvement in therapeutic efficacy within a pancreatic cancer tumor model. Significantly, inhibiting VEGF-receptor 2 has demonstrated the capability to decrease vascular leakiness, normalize the basement membrane structure, and reduce the number of dilated and tortuous vessels[72]. Tumor priming has been validated as a means to boost vascular permeability, markedly enhancing the absorption of paclitaxel-loaded polymeric micelles (20nm), doxorubicin-loaded liposomes (100nm), and targeted paclitaxel-loaded nanoparticles (230nm)[73]. Like vascular normalization therapies, the effective application of chemotherapeutic priming requires meticulous optimization of dosage and scheduling to facilitate the efficient uptake of nanoparticles by tumors. The design of nanoparticles can be customized to align with specific phenotypic features of tumors, such as biomarker expression, extracellular matrix (ECM) density, hypoxia levels, and vascular physiology. Complementary approaches for modifying the tumor microenvironment can be chosen to match the selected nanoparticle type, resulting in enhanced therapeutic outcomes[74]. Moreover, the prospect of combining two distinct priming strategies holds potential for simultaneously targeting different components of the tumor microenvironment.

16. CHALLENGES AND LIMITATIONS

PCT has implemented a framework akin to "Individualized Cancer Therapy" (ICT) for tailoring cancer treatment strategies. This holistic approach includes elements such as drug sensitivity testing, cancer biomarker analysis, bioinformatics detection, pharmacogenetics, personalized antimetastatic therapy, consideration of drug combinations, chemotherapy support, cost-effectiveness evaluation, and guidelines for molecular diagnosis utilization and reimbursement[75] . The challenge in managing cancer progression stems from the inappropriate selection and administration of anticancer agents. Researchers and clinicians increasingly turn to PCT to improve therapy quality and outcomes by prescribing the most suitable and effective drugs. The integration of genetic, molecular, and bioinformatics data, along with contemporary experimental methods, enhances the identification of oncogenes with unprecedented accuracy. Unfortunately, current treatment protocols provide extended survival benefits to only a limited subset of cancer patients. Overcoming this hurdle necessitates the development of innovative, strategic, and precise technologies, representing a crucial step toward significant progress in clinical oncology. In contrast to clinical investigations, preclinical models excel in incorporating tumor–stroma interactions and identifying potential markers for subsequent medical validation[76]. Cell lines, a potent tool in cancer research, facilitate the exploration of genetic drivers or suppressors of human malignancies, as well as multiple markers associated with therapeutic response.

17. CONCLUSION

Resistance mechanisms against traditional cytotoxic chemotherapeutics and targeted therapies designed for specific molecules share commonalities, involving activated prosurvival pathways and impaired apoptotic machineries. These shared factors collectively contribute to response variability, underscoring the need for precise treatment strategies. The tumor microenvironment's (TME) considerable influence on modulating tumor sensitivity is increasingly recognized as a pivotal factor in advancing contemporary anticancer therapeutics. The responsiveness or resistance of malignancies to particular pharmacological agents hinges not solely on intrinsic traits of cancer cells but also significantly on the contextual intricacies of the specific TME. In the realm of precision cancer therapy (PCT), the clinical goal is to target abnormalities guiding tumor growth and survival by administering customized drug combinations for each individual patient. The growing feasibility of this objective is facilitated by rapid advancements in cutting-edge technologies dedicated to tumor characterization and the expanding repertoire of therapeutic agents designed to target elements within the TME. Despite progress, challenges persist in seamlessly integrating targeted therapy into the microenvironment to enhance the effectiveness of radiation therapy in clinical contexts. Overcoming these obstacles will not only deepen our understanding of the mechanisms governing radiation therapy in cancer treatment but also pave the way for ongoing progress in this therapeutic approach. The tumor microenvironment plays a crucial role in the initiation, expansion, development, and spread of tumors, orchestrating intricate interplays among tumor cells, stromal tissue, and the extracellular matrix. The landscape of cancer therapy appears poised for transformation through the creation of pharmaceutical agents tailored to specifically target these crucial constituents. Despite dedicated efforts

invested in exploring tumor treatments in recent decades, cancer remains a significant threat to human well-being. There seems to be a noticeable lack of substantial progress in improving the survival rate, prompting an urgent need for both experimental and clinical research to unravel the fundamental mechanisms underlying this challenge.

18. AUTHORS CONTRIBUTION STATEMENT

Somenath Ghosh, Devika S Kumar conceptualized the manuscript and gathered the data. Ratna Kumari Nitta, Nilima Gajbhiye and M. Helan Soundra Rani analyzed the data and provided the necessary information regarding the research design. All the authors revised the manuscript critically and approved it before submission.

19. CONFLICT OF INTEREST

Conflict of interest declared none.

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