Review

The Interaction of Immune System in Tumour Microenvironment and Possible Role of Cancer Cell Immnunosensitization for Better Treatment Efficacy: A Review

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ABSTRACT

Unlike haematologic malignant cells which express-cell surface common antigens uniformly and are susceptible to targeted cancer immunotherapy, solid tumours either lack such antigens or have been mutated due to chemotherapy or other therapeutic interventions. Moreover, rapidly dividing tumour cells present–complex and dynamic tumour metabolism, which hampers immune cells' reactivity against the tumour cells. Hence solid tumours other than immune-sensitive cancers such as melanoma and renal cell carcinoma are less responsive towards current cellular immunotherapy strategies, including cytokine therapy, dendritic cell-based vaccines, and immune-activating antibodies. Nonetheless, emerging evidence supports combined approaches that target immunosuppressive or antiapoptotic molecules, involving sensitization of the cancer cells by immunosensitizing drugs to express specific ligands that will be recognized by the immune cells via trafficking. This review highlights the immune system's involvement in the tumour microenvironment and the potential significance of cancer cell immunosensitization for improved treatment outcomes.

Key words: Immunosensitization, immunotherapy, tumour immuno-resistance, tumour microenvironment

INTRODUCTION

Cancer is the leading cause of death in the United States. The pattern is mostly due to urban lifestyle aspects including smoking, excessive alcohol consumption, stress, and obesity, which elevate the risk of chronic diseases including cancer. In addition, it is the second leading cause of mortality in children under 14, after car accidents, and the fourth in adolescents between 15-19 years old (Siegel *et al*., 2021). Over several decades, 1 in 285 children and adolescents were diagnosed with cancer. Recently, the American Cancer Society reported that 1 in 260 people are suffering from cancer (Nierengarten, 2023). Surgery, radiation, and chemotherapy are the main solid tumour treatments for children. Localized and non-metastatic tumours benefit from surgery however, incomplete resection can lead to cancer recurrence. Approximately, half of the cases of malignancy including childhood are attributable to solid tumours such as sarcomas, carcinomas, and lymphomas, with the most common being brain tumours, lymphoma, neuroblastoma, Wilms' tumour, and osteosarcoma. Although such tumours arise from diverse heterogeneity from that seen in adults (Jones *et al*., 2019) the unique physiology of solid tumours generally stems from the tumour vasculature. Normal blood vessels

consist of arterioles, capillaries, and venules that are evenly spaced and well-differentiated (Atherton & Hinen, 2022) conversely, the tumour vasculature displays an irregular pattern of disorganization, primarily due to the uncontrolled growth of the neoplastic cell population and the overexpression of pro-angiogenic factors (Barachini *et al*., 2023). Tumour vascular irregularities slow blood flow, making them "leakier" than normal tissues and causing tumour hypoxia and necrosis, which hinders cancer treatment. (Sørensen & Horsman, 2020). As advances in immunotherapy proved to be successful in ameliorating haematologic malignancies (Murad *et al*., 2018) similar immune-oncology approach has been directed towards solid tumours. Unfortunately, the complex and dynamic metabolism of the rapidly dividing tumour cells (Chen *et al*., 2017) in addition to the heterogeneous interaction of their micro-vessels with the tumour microenvironment imposes many challenges, particularly the tumour immuno-resistance.

Tumour cells resistance to immunotherapies is mainly attributable to the inhibition of the immune cells by altered cancer cell metabolism, caused either by dysregulation of tumour metabolism via the Warburg effect (Augustin *et al*., 2020) or immune infiltration barriers due to extracellular matrix (ECM) remodeling (Mushtaq *et al*., 2018). Solid tumours were often less responsive to current cellular immunotherapy strategies, including cytokine therapy, dendritic cell-based vaccines, and immune-activating antibodies. Nonetheless, ongoing studies towards combinatorial approaches, employing immunosensitizing drugs capable of inducing the expression of specific ligands on the malignant cells for recognition by the immunosuppressive cells during immune cells trafficking (Volpedo *et al*., 2021). Targeted immunotherapy that efficiently sorts cancer cells from normal cells and kills them with apoptotic immune cells requires such an initiative. This review emphasizes the role of the immune system in the tumour microenvironment and the potential importance of cancer cell immune sensitization for enhanced treatment outcomes. Recognizing the significance of the connection between the tumour microenvironment (TME), the immune system, and the treatment of cancer has resulted in the discovery of new possibilities for the development of more effective and targeted therapy for cancer patients.

Tumour microenvironment towards oncogenic tumour metabolism

Tumour microenvironment (TME) refers to the network of cells and structures surrounding the tumour cell, comprised mainly of heterogeneous cell types including immune cells, proliferating tumour cells, infiltrating inflammatory cells, blood vessels, lymphatic vessels, and fibroblasts (Shishir *et al*., 2018). These cells exist within a complex association and are thus pivotal for cancer cell progression involving cancer cell survival, migration, metastasis, chemoresistance as well as immune-resistance (Bussard *et al*., 2016). Although metabolic reprogramming including oncogene activation, inactivation of tumour suppressor genes as well and mutation of glycolytic enzymes are intrinsic to disease progression (Miranda-Gonçalves *et al*., 2018), recently, regulation of TME in tumour metabolism gained similar importance.

Essentially, tumour metabolism refers to the Warburg effect, which describes cancer cells' preference towards the glycolytic pathway rather than the oxidative phosphorylation, even in aerobic conditions (Fan *et al*., 2019). Due to rapid growth and defective perfusion of the blood vessel, tumour-associated hypoxia exacerbated cellular glycolysis hence anaerobic lactic acid accumulation in the tumour microenvironment (de la Cruz-López *et al*., 2019). Indisputably, acidosis and hypoxia are touted as the biochemical hallmark of TME which poses a profound role towards modulation of cancer cell metabolism hence disease progression. Moreover, high interstitial fluid pressure and increased extracellular matrix (ECM) stiffness are also characteristic features of the TME (Justus *et al*., 2015) with factors such as reactive oxygen species (ROS), growth factors, cytokines, and metabolites associated with their roles toward modulation of the TME (Ura *et al*., 2018).

Tumour cells recruit stromal, immune, and vascular cells by secreting growth factors, chemokines, and cytokines with subsequent release of growth factors and intermediate metabolites for tissue remodeling toward the new microenvironment. The dynamic interaction between cancer cells and their microenvironment promotes rapid cell proliferation and eventually cancer metastasis (Sun *et al*., 2018). Oxygen and nutrition availability may also alter TME metabolic pathways (Nagarajan *et al*., 2016). Tumour cell's energy needs and high levels of glycolytic intermediates were sustained by enhanced glucose uptake through high levels of glucose transporters, lactate dehydrogenase, and other glycolytic enzymes (Forkasiewicz *et al*., 2020). Nonetheless, a high level of lactate leads to acidic conditions, reactive oxygen species (ROS) production, and MAPK signaling activation, subsequently elevating the metabolic capacity of tumour cells. Thus inhibition of the glycolytic pathway imposes TME remodeling, as a previous study reported low expression of Interferons (IFN) and Fas ligand (FasL) following inhibition of both glycolysis and oxidative phosphorylation, indicating modulation of TME metabolism by NK Cells (Wang *et al*., 2020). Hypoxia in tumour cells stimulates angiogenesis due to increased expression of vascular endothelial growth factor (VEGF) resulting in oncogenesis transformation (You *et al*., 2021). Besides having potent vascular endothelial mitogenic activity, VEGF also induces vascular hyperpermeability (Katayama *et al*., 2019) which favors the migration of endothelial cells through the extracellular matrix (Aguilar-Cazares *et al*., 2019).

Interaction of the immune system with tumour microenvironment

The human immune system's comprehensive network comprises immune cells, cytokines, lymphoid tissues, and organs which synergistically eliminate pathogens while protecting against foreign molecules. NK cells, neutrophils, macrophages, T cells, and DCs, together with non-immune stromal cells such as fibroblasts and endothelial cells, could penetrate the tumour and modulate the TME.

Immune cells block tumour growth in the early stages of the disease, but as the tumour grows, they seem to support cancer progression and thus resistance to treatments (Parker *et al*., 2015; Ugel *et al*., 2015; Kalinski & Talmadge, 2017). The immune cells facilitate tumour progression either by inducing an immunosuppressive, tolerogenic environment or by mediating ECM breakdown and angiogenesis (Kitamura *et al*., 2015). Previous studies have shown that tumour necrosis factor (TNF)-α supports the survival and proliferation of tumour cells and increases vascular permeability (Patel *et al*., 2018)

Metastatic breast, colorectal, and prostate cancer patients had higher circulating NK cells than healthy donors, indicating enhanced activity against cancer cell proliferation (Dianat-Moghadam *et al*., 2020). The NK cells were found capable of recognising and intercepting circulating tumours in the bloodstream hence killing them before migration and subsequently halting metastasis (Chiossone *et al*., 2018). Moreover, NK cells can eliminate tumours with reduced or absent MHC-class I expression that evades CD8+ T cell-mediated control (Lang *et al*., 2020). Nevertheless, tumour cells have developed several mechanisms to escape NK cell immunosurveillance by modulating cell surface molecules involved in their identification and releasing immunosuppressive soluble factors such as TGF-β, prostaglandins, and adenosine in the TME (Bassani *et al*., 2019). Following exposure to TGF-β, NK cells from healthy donors show a change in their killing capability due to suppression of perforin and granzyme release (Zaiatz-Bittencourt *et al*., 2018). Other studies reported that surface transporters, particularly glucose transporter member 1 (GLUT1), assist NK cells by transporting glucose into cells for the generation of ATP and pyruvate, via glycolysis and oxidative phosphorylation (Piątkiewicz *et al*., 2016).

Besides NK cells, neutrophils play an important role in the infiltration of inflammatory cells in various cancer types (Coffelt *et al*., 2016) indicated by the significant levels of neutrophilia in the blood of advanced cancer patients (Shaul & Fridlender, 2018). Neutrophils, like all leukocytes, travel from the blood into tissues under the effects of particular chemokines and cytokines that promote tumour angiogenesis and cancer cell dissemination. (Coffelt *et al*., 2016). It was shown that UV irradiation-induced metastasis of primary melanoma was mediated by activated neutrophils, which stimulate angiogenesis and TNF-dependent migration of melanoma cells towards vascular endothelial cells *in vitro* and *in vivo* (Bald *et al*., 2014). The exact cause of neutrophilia in cancer patients is unclear, however, solid tumours emit cytokines that decrease circulating neutrophils (Shaul & Fridlender, 2019).

Dendritic cells (DC) are another type of immune cell, which serve as sentinels for the immune system, coordinating both innate and adaptive immune responses mostly present in peripheral tissues and immunological organs such as the thymus, bone marrow, spleen, lymph nodes, and Peyer's patches. They function by sampling the peripheral tissues where they recognize, engulf, and process pathogens, presenting pathogen-derived antigenic peptides in the form of major histocompatibility molecules (MHCs) to naive T lymphocytes at lymphoid organs. Through these processes, DCs form a critical link between innate and adaptive immunity essential for the development of antigen-specific immune responses. However, suppressive signals in the tumour microenvironment can interfere with DC's anti-tumour action (Audiger *et al.,* 2017).

Meanwhile, regulatory T cells (Tregs), comprised of a heterogeneous population of T lymphocytes are also involved in immune responses. The immunosuppression of Tregs, natural killer (NK) cells, CD8+ T cells, and antigen-presenting cells has been considered a major way, which help tumour cells escape from immune surveillance. Tregs working in concert with tolerogenic DCs, play critical roles in the establishment and maintenance of an immunosuppressive TME to inhibit anti-tumour immunity (Janikashvili *et al*., 2011). Expression of inhibitory receptors by Tregs exerts their suppressive function on DCs through different mechanisms. A recent study reported that Tregs are essential to self-tolerance and homeostasis, and they can even stimulate metastasis directly (Seifert *et al*., 2020). Moreover, Treg-produced suppressive cytokines such as transforming growth factor (TGF) and interleukin-10 (IL-10) decrease immune responses directly (Okeke & Uzonna, 2019). The summary of immune cells' interactions with tumour cells is shown in Figure 1.

Mechanism of tumour cells' resistance to immunotherapies

Cancer immunotherapy, also known as immuno-oncology, is a type of cancer treatment in which the body's immune system is used to prevent, control, and eradicate cancer. Immunotherapy is gradually evolving into a distinct therapeutic entity, contributing as the fifth pillar of cancer management alongside surgery, radiation, chemotherapy, and targeted therapy. In cancer, the immune system serves a dual purpose. It provides protective immunity whilst still facilitating malignant progression, either by shaping tumour immunogenicity or by establishing a microenvironment that can stimulate tumour growth that leads to metastatic cascade (Wagner & Koyasu, 2019).

Therapy resistance also can be caused by tumour cells' intrinsic factors, such as the tumour

cell's characteristics, or tumour cell-extrinsic factors, such as cells in the stroma of the tumour microenvironment. Primary resistance to immunotherapies has been associated with an increase in the number of regulatory T (Treg) cells, myeloid-derived suppressor cells (MDSCs), M2 macrophages, and pro-tumour N2 neutrophils (Capone *et al.*, 2018; Zer *et al.*, 2018; Melief *et al.*, 2019). Although a detailed picture of how these immunosuppressive cells contribute to immunotherapy resistance is still missing, various underlying mechanisms have been proposed. IL-10 and TGF-*β* can limit local T cell priming through the suppression of both DC function and the proliferative capacity of T cells (Fu & Jiang, 2018).

The expression of immune checkpoints (ICs) which includes programmed cell death ligand-1 (PD-L1) and Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) at the surface of these immune suppressive cells provides them with the means to inhibit local T cell activation directly. Furthermore, TNF-α in the TME may also have a downside as it can bind to TNFR2, which is expressed by regulatory Treg cells and MDSCs to protect them from TNF-α induced death, while in the same way reducing the capacity of M1 macrophages to clear tumour cells. Taken together, Treg cells, M2 macrophages, MDSCs, and N2 neutrophils may suppress effector T cells systemically and in the TME, resulting in primary resistance mechanisms during cancer immunotherapy. In addition to tumour-infiltrating immunosuppressive immune cells, the fibroblasts in tumours contribute to therapy resistance. One important driver of fibroblast activation in the TME is TGF-β, an immunosuppressive mediator found to interfere with the anti-tumour immune response. The TGF-β-driven activation of fibroblasts gives rise to a specific phenotype of immunomodulatory cancer-associated fibroblasts (CAFs).
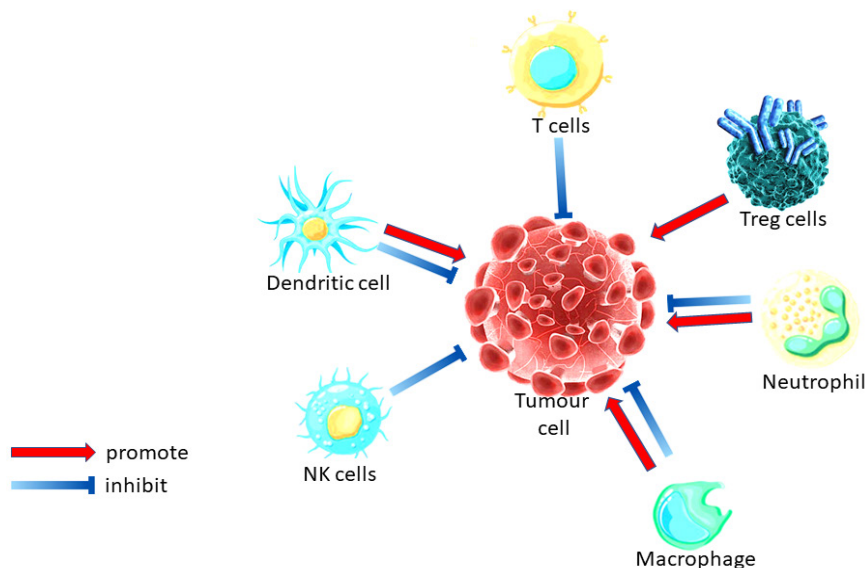

Fig. 1. Immune cell interactions with malignant cells in a tumour. Within the context of the tumour microenvironment, immune systems can act by either promoting or inhibiting tumour growth. The function of the immune cells will also change depending on the types of cells that are present in the tumour tissues.

Traditional chemotherapeutic drugs are cytotoxic and target rapidly multiplying cells, a characteristic of cancer cells. However, cells in the bone marrow, digestive tract, and hair follicles can also be damaged, leading to symptoms such as myelosuppression, nausea, vomiting, and hair loss (Oun *et al.*, 2018). The prerequisite for effective drug activity is adequate drug transport to the target site, which is dependent on the blood flow in the tumour bed and the drug's diffusion properties in tissue. However, delivery may be regulated by the degree of plasma protein binding, oral drug absorption, and first-pass metabolism in the liver via multiple mechanisms. Blood flow across a capillary bed is related to the difference in arterial and venous pressures and inversely proportional to geometric and viscous resistances. More targeted cancer drug discovery has led to a rise in the variety of cancer treatment methods available to oncologists. Continued research on the design of successful oncology medications for use in chemotherapy has enhanced our understanding of their mechanism of action, broadened their activity/function range, and unlocked new uses for better patient outcomes.

Traditional drugs target several different entities: nucleic acids, metabolic and signaling enzymes, and microtubules. DNA is a prominent target for therapeutic research since it is the bearer of

genetic information and is involved in carcinogenesis and pathogenesis. The key steps in cell growth and division are DNA replication, transcription, and protein synthesis. A drug's maximal specific DNA binding affinity is always a difficulty. Additionally, the medicine should not impair normal cells' cellular and nuclear transport activities. When combined with other anticancer treatments with distinct modes of action, several of the most effective anticancer medications that target DNA have been shown to significantly improve survival rates in cancer patients (Mokhtari *et al.*, 2017). Apart from DNA, RNA, enzymes, and other proteins all contribute significantly to the development of anticancer drugs (Kumar *et al.*, 2015). DNA synthesis is the hypothesized cause of cell death when targeting nucleic acids. The most well-known DNA binding processes include the alkylation of nucleophilic regions in the double helix. The cross-linking of double-stranded DNA produced by the bifunctional alkylating chemicals impairs DNA replication as well as apoptosis (Yimit *et al.*, 2019).

Role of immunosensitizing drugs in cancer diseases

Technological advances such as modern molecular biology methods, high-throughput screening, structure-based drug design, and combinatorial and parallel chemistry on top of full human genome sequencing significantly aided the process of drug discovery over the past five decades, resulting in medications with improved efficacy against cancer. Moreover, targeted therapies, are intended to attack cancer cells while causing less harm to normal cells.

Drugs can be transported across the plasma membrane by a variety of methods, including passive diffusion, assisted diffusion, and active transport systems (Fong, 2015). Passive diffusion of pharmaceuticals across the plasma membrane's bilayer lipid structure is a function of the drug molecule's size, lipid solubility, and charge. Numerous anticancer therapies require activation before exerting their lethal action. Regardless of their origin or method of action, cytotoxic anticancer drugs can be categorized according to their targets. Cisplatin, cyclophosphamide, fluoropyrimidine, gemcitabine, and methotrexate are a few chemotherapeutic drugs that are used in chemotherapy (e.g., irinotecan & camptothecin). Severe systemic toxicity and drug resistance will be experienced if the dosage of chemotherapeutic agents is increased. Often, cancer treatment effectiveness is hampered by chemotherapy drug accumulation in the tumour (Tafesse *et al.*, 2020). Moreover, the drug's side effects may restrict a patient's capacity to continue treatment. Recently, a large amount of research has focused on producing more potent and selective anti-cancer medications, or on devising new delivery methods for the treatments.

Different routes of administration have been employed in attaining unique pharmacological targets. The regional administration is used to target the drug specifically to the tumour location and thus increases drug concentration near the tumour (Senapati *et al.*, 2018). Pharmacokinetic outcomes are more consistent when injected subcutaneously or intramuscularly. For localized and disseminated diseases, the most common mode of drug administration is intravenous infusion. Intravascular delivery, such as intraarterial infusion of fluorodeoxyuridine for the treatment of liver disorders, offers a pharmacologic advantage. Nonetheless, it is associated with variable medication bioavailability in and among patients (Jacobs *et al.*, 2017). Most late-stage malignancies are treated with chemotherapy. It is also used in early cancer to minimize tumour size and reduce the likelihood of recurrence (DeSantis *et al.*, 2014). The geometric resistance to blood flow increases with tumour size, which may impede drug and oxygen delivery to large tumours, reducing the efficacy of chemotherapy or irradiation treatment (Graham & Unger, 2018).

Inflammatory illnesses, autoimmune diseases, viral diseases, atherosclerosis, and cancer are all linked to immune system failure (Lombardi *et al.*, 2018). For the treatment of these illnesses, several medicines that directly target the immune system have been created. Immune checkpoint inhibitors (ICIs), for example, have significantly improved the prognosis of patients with various malignancies by modifying their immunosuppressive status and increasing antitumour immunity (Ribas & Wolchok, 2018). Monoclonal antibodies are used in ICIs and many other targeted anticancer medicines, making them quite pricey.

Considering the lengthy duration and high expenses of the clinical studies required for regulatory approval by the United States Food and Drug Administration (FDA), it is clear that alternative tactics are required to be developed. Even though the rising cost of new drug development and the decreasing number of truly efficient medicines approved by the US Food and Drug Administration (FDA) pose unprecedented challenges for the pharmaceutical industry and patient healthcare, including oncology (Coussens *et al.*, 2017), they also present unprecedented opportunities. As a result of the increasing availability of FDA-approved drugs and quantitative biological data from the human genome project, several strategies have been proposed to shorten the drug development process and significantly reduce costs, including drug repurposing (Ekins *et al.*, 2019), network pharmacology (Poornima *et al.*, 2016) other approaches.

A previous study using a combination of liposomal doxorubicin, bevacizumab, and temsirolimus (DAT) for patients with advanced cancers was designed to test the preclinical rationale that anthracycline resistance is driven by upregulation of hypoxia-inducible factor alpha (HIF-1), which promotes tumour

survival and angiogenesis. Angiogenesis inhibition, such as with the VEGF inhibitor bevacizumab, may thus be used to overcome anthracycline resistance. Upregulation of HIF-1, on the other hand, contributes to bevacizumab resistance. Temsirolimus, a powerful inhibitor of mTOR and, as a result, HIF-1, can be used to overcome this resistance (Faes *et al.*, 2017).

Millions of patients have been prescribed statins to decrease blood lipids to prevent coronary heart disease. Additionally, along with their cholesterol-lowering effects, numerous investigations have demonstrated that statins have immunomodulatory activities via mevalonate-independent and -dependent mechanisms (Sarrabayrouse *et al.*, 2017). They suppress the activity of GTPases belonging to the Ras and Rho families, which govern a variety of cellular activities, including cell death, metastasis, and immunological responses (Palomino-Morales *et al.*, 2016). Statins also affect the immune system by inhibiting the generation of pro-inflammatory cytokines and activating CD8+ T cells (Côté-Daigneault *et al.*, 2016). On another note, metformin is a commonly used antidiabetic medication made from the plant Galega officinalis, which suppresses hepatic glucose synthesis in people with type 2 diabetes (Tao *et al.*, 2019). Ubiquinone oxidoreductase situated in the mitochondrial membrane activates activated protein kinase (AMPK) and suppresses gluconeogenesis. Both drugs are cost-effective and may be administered safely since their side effects are well-documented. If the immunomodulatory effects of these previously approved medications can be proven, combinatorial usage of these treatments may be able to improve the effects of traditional cancer therapy (Popovic *et al.*, 2018). As mentioned earlier, metformin can be used for the treatment of cancer, whereby it was shown to improve the number and activity of tumour-inflating lymphocytes (TILs) (Xu *et al.*, 2019). Another study reported by Pereira *et al.* found that metformin contributes to stronger immunomodulatory effects and hence lowers the metastasis rate of melanoma cells by lowering the stability and membrane location of programmed death ligand 1 (PD-L1) and boosts Cytotoxic T lymphocytes (CTLs) activity (Pereira *et al.*, 2018).

In addition, thalidomide and its variants, lenalidomide and pomalidomide, are used to treat multiple myeloma, a plasma cell tumour (Chim *et al.*, 2018). Thalidomide initially gained attention for its direct tumouricidal effects on myeloma cells via cell cycle arrest, as well as its antiangiogenic capabilities. Due to its immunological effects, it was later classified as an immunomodulatory drug (IMiD) (Matsushita & Kawaguchi, 2018). Moreover, certain conventional anticancer agents, such as anthracyclines or alkylating agents, have been shown to induce immunomodulatory effects on a variety of cancer cells by increasing calreticulin (CRT) expression on the cell surface, followed by the release of high mobility group box 1 (HMGB1), ATP, annexin A1, and type I interferon from cancer cells (Vacchelli *et al.*, 2015). Through CRT expression and HMGB1 secretion, mouse vaccination trials with cancer cells pre-treated with chemotherapeutic medicines such as doxorubicin or mitoxantrone have demonstrated effective cancer regression (Matsushita & Kawaguchi, 2018).

Clinical evidence supports these findings, demonstrating that calreticulin (CRT) expression improves cancer patient prognosis (Fucikova *et al.*, 2016). These findings suggest that some chemotherapeutic treatments not only kill cancer cells directly but also stimulate patients' immune responses against cancer cells, therefore contributing to cancer cell elimination. Anticancer drugs like EGF receptor inhibitors also trigger immune responses against cancer cells through ICD. The promoter region of tumour suppressor genes is typically hypermethylated, silencing them. Hypomethylating agents (HMAs) cause epigenetic modification of cancer-related genes, hence they can be expected to be effective in cancer treatment (Héninger *et al.*, 2015).

Systemic drug toxicity and inefficiency are primarily caused by a lack of targeted medication delivery to neoplastic tissues. Tumour-targeted treatment therefore becomes an important issue in cancer therapy, since it would overcome side-effects and make anti-neoplastic medicines fully effective. In this context, the results of better medication delivery have been seen as promising based on passive and/or active (or receptor-mediated) tumour targeting. Anti-apoptotic proteins enable cancer cells to avoid cell death. Classic chemotherapy drugs work by inducing apoptosis in cancer cells.

Chemotherapy-induced apoptosis has been avoided by several tumours. Higher protein tyrosine kinase expression, for example, has been linked to resistance to induced apoptosis in small-cell lung cancer (Tan *et al.,* 2018). Research showed that the TGF pathway, in combination with IL-10, appears to have a role in immune regulation in several different ways. TGF-1 is a growth factor. Increased production of interleukin-10 (IL-10) and chemoattractant protein (MCP-1) by TGF-1 results in increased tumour infiltration and immune inhibition. Initially, CTLA-4 was explored in cancer patients because it suppressed tumour development in mice in preclinical studies. This was the first checkpoint inhibitor approved by the United States Food and Drug Administration (FDA) for metastatic melanoma, with a 10-month improvement in median overall survival (Chae *et al.*, 2018). This medication has been studied in different cancers but does not fulfill defined clinical endpoints. Other solid tumours benefitted from targeting the PD-1 receptor/ligand PD-L1 pathway using new and more effective anti-PD-1 antibodies. Many anti-inflammatory drugs have been studied in solid tumours. Jak inhibitor ruxolitinib is approved for myeloproliferative neoplasm (Qureshy *et al.*, 2020). Tocilizumab, a monoclonal antibody that binds to the IL-6R, has been studied in ovarian cancer patients together with carboplatin/PLD and interferon-2b (Dijkgraaf *et al.*, 2015). Since this drug inhibits IL-6R and increases soluble IL-6R, it has low toxicity and may improve survival. It is presently being investigated in pancreatic cancer with chemotherapy.

CONCLUSION

In a nutshell, tremendous progress has been made in understanding the role of the immune system in driving the development of cancer, including immune sensitization particularly involving solid tumours. Advances in immunology have sparked the development of new therapeutics with enormous potential for treating human cancers. Recently, targeting immunosuppressive mechanisms by sensitizing the cancer cells to express specific ligands for immune cell trafficking has been widely research. Targeting these essential immune cells sensitizers is a crucial step in anticancer treatment development in the future. In addition, using multitargeted techniques could enlighten researchers to elucidate the essential factors that control TME in cancer treatment. In addition, using immune cell markers to predict cancer outcomes and targeting diverse immune system components to induce an anti-tumour immune response have influenced and will continue to influence cancer treatment. A comprehensible combination of different strategies appears more effective than single methods, due to the tumour heterogeneity. This is due to the consequences of a variety of signaling pathways or crosstalk that exist in the network of cancer cell communication. Though more research is needed to better understand the mechanisms of drug-induced toxicities, these new therapies have resulted in better cancer treatments.

ETHICAL STATEMENT

Not applicable.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interest.

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