Strategies for cancer therapy: targeting tumor microenvironment and nanotechnology

Abeer H. Abdel-Halim

Department of Biochemistry, Biotechnology Research Institute, National Research Centre, Giza, Egypt

Correspondence to Prof. Dr. Abeer H. Abdel-Halim, Professor of Biochemistry, Department of Biochemistry, Biotechnology Research Institute, National Research Centre, 33 El-Bohouth Street, El-Dokki, PO Box 12622, Giza, Egypt. Tel: +20 109 772 2221; fax: +20 233 370 931; e-mail: abeer.hamed@yahoo.com

Received: 24 December 2022
Revised: 5 February 2023
Accepted: 6 February 2023
Published: 17 May 2023

Egyptian Pharmaceutical Journal 2023, 22:165–176

Cancer is still a serious health problem globally. Conventional therapies have adverse effects, which affect human life quality. Tumor microenvironment (TME), also known as surrounding stroma, has a contributory role in cancer development. Understanding the interaction between TME and cancer progression is a challenge and helps to develop new therapeutic strategies that neutralize the tracks taken by cancer cells to grow, spread, and resist therapy. Therefore, targeting TME components may be effective in improving tumor therapy. Using nanotechnology for drug delivery is of great interest, where it overcomes some obstacles such as solubility and absorption of drugs and delivering them to the appropriate place of action. The main target of nanotechnology for drug delivery is the ability to differentiate between normal and cancer cells. It can be concluded that TME is an important complementary strategy for the development of anticancer drugs. Multitargeted therapy has better efficient potential than individual therapy against cancer.

Keywords:
drug delivery, extracellular matrix, fibroblasts, macrophages, nanotechnology, tumor microenvironment

Egypt Pharmaceut J 22:165–176

1687-4315

Introduction

Cancer is still a burden health problem worldwide. It is the second leading cause of death after cardiovascular diseases, where it was responsible for nearly 10 million deaths in 2020. The commonest type of cancer is breast cancer (2.26 million cases), followed by lung cancer (2.21 million cases), with the highest mortality rate (1.8 million deaths) globally [1]. In Egypt, liver cancer has the highest incidence rate (33.6% among men), followed by breast cancer (32% among women). In comparison to 2013, the incidence rate will more than triple by 2050 [2]. The number of new cases for all cancers in Egypt in 2018 were ~134 632 new cancer cases, with 89 042 deaths owing to cancer [3]. Figure 1 shows the percent of new cases for all cancers in Egypt. There is a strong link between behavioral factors and a variety of malignancies, where smoking, alcohol consumption, radiation, lack of physical activities, unhealthy diet, and obesity are risk factors for cancer, besides chemicals and toxic substances, chronic infections, and aging. Cancer prevention is the main way to reduce cancer burden through environmental intervention and lifestyle [4,5].

Most human cancers share a group of events that include uncontrolled growth by inhibiting tumor suppressor genes; oncogene activation for activating their own growth; genome instability; inhibition of apoptosis and immune system; induction of angiogenesis; and activation of invasion and metastasis [6]. All these hallmarks represent mechanisms of tumor cells to inhibit the cytotoxic effect of chemotherapy, which is known as drug resistance [7]. Tumor microenvironment (TME), also known as surrounding stroma, has a contribution role in cancer development. Understanding the interaction between TME and cancer progression is an important complementary strategy for the development of anticancer drugs.

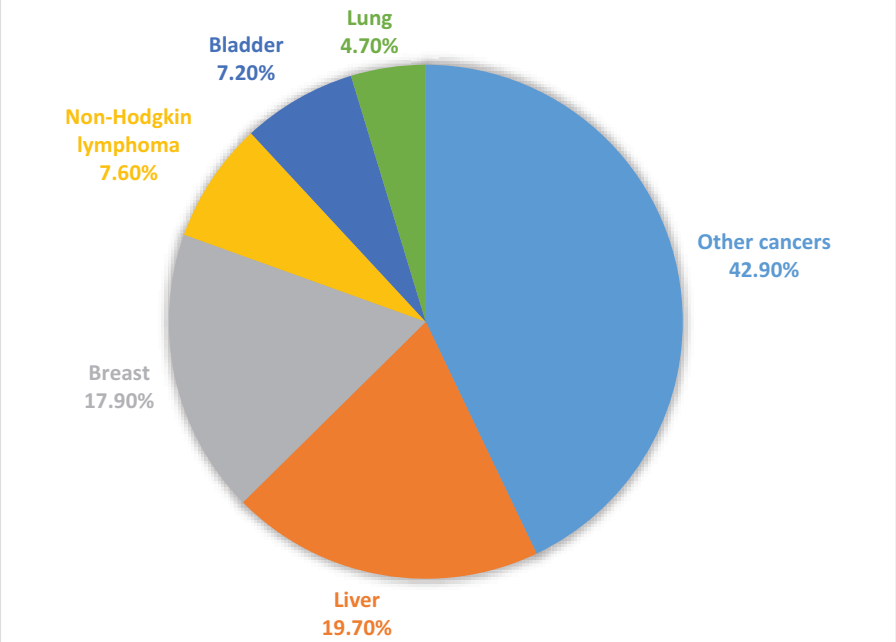
Methods

Articles that are involved in this work were selected in relation to TME and its targeting for cancer prevention and the development of techniques that enable the delivery of therapeutic agents into cancerous cells with minimal or no effect on normal cells. They were reviewed stringently, and then the manuscript was designed.

Role of tumor microenvironment in carcinogenesis

TME, also known as surrounding stroma, is a set of components that surround the tumor. The crosstalk between tumor cells and TME leads to tumor development and progression [8,9]. TME has been

Figure 1



The most abundant cancer in Egypt.

discovered with the proposal of the 'seed and soil' theory in 1889, whereby the cancer cell (seed) needs a site to grow and metastasize [10,11]. Immune cells, extracellular matrix (ECM), and stromal cells such as mesenchymal stromal cells, epithelial cells, lymphatic endothelial cells, vascular cells, cancer-associated fibroblasts (CAFs), pericytes, and adipocytes comprise the TME [12,13]. The interaction between tumor and its microenvironment, which through the secretion of cytokines, chemokines, and other signaling factors (as matrix remodeling enzymes, growth factors, and inflammatory mediators), can determine the fate of cancer cells if they are eradicated, metastasized, or have therapeutic response or drug resistance. These inflammatory mediators may have resulted from intrinsic and extrinsic pathways. The intrinsic one resulted from genetic alteration of neoplastic cells, whereas the extrinsic one resulted from the immune cells like macrophages and T cells [14,15]. Studying the relationship between a tumor and its microenvironment will help to improve therapeutic drugs that target one or more TME components, which can improve patient outcomes [16].

Figure 2 shows the interaction between the tumor and its microenvironment. TME is characterized by an acidic pH, hypoxia, and an elevation of interstitial fluid pressure. As cancer size increases, the cells that are found within the tumor get depleted of oxygen. The lack of oxygen causes genetic instability, which causes cancer development, ECM stiffness, and an increment of hypoxia-inducible factor 1 alpha, which activates angiogenesis and increases the rate of glycolytic behavior, which is the production of lactate from glucose in spite of the presence of oxygen (Warburg effect). Lactic acid production results in an acidic microenvironment, which induces degradation of ECM and increased cell migration [17,18].

Tumor microenvironment components

Stromal cells

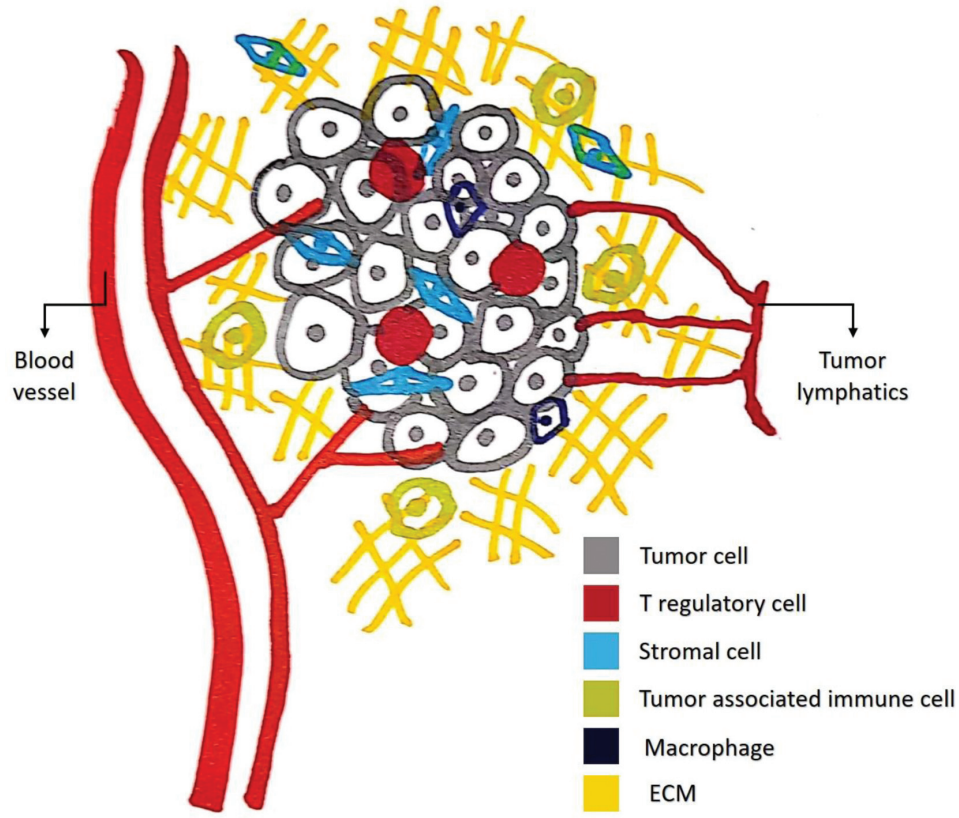
The stromal cells (nonmalignant) around the tumor represent ~90% of TME, whereas tumor represents 10%. The main abundant cells of TME are CAFs [8].

Carcinoma-associated fibroblasts

CAFs are the main component of TME; they originate from resident fibroblasts, cancer cells, smooth muscle cells, or bone marrow mesenchymal stem cells [19]. Highly active CAFs can regulate epithelial tumor cell metabolism and cancer stem cell plasticity and stimulate cell migration, inflammation, and proangiogenic signals. Their transformation was in response to a paracrine signal [19,20].

They suppress immune cells such as natural killer (NK) cells and cytotoxic T cells via secretion of transforming growth factor-β (TGF-β) and interleukin 10 (IL-10) [21]. They secrete ECM components and remodeling enzymes, which causes the release of growth factors

Figure 2



Tumor microenvironment.

(insulin growth factors I and II) that promote growth, invasion, and metastasis [21,22]. They feed lactic acid to cancer cells where this catabolite transfer allows cancer cells to produce ATP (reverse Warburg effect) [23]. They induce angiogenesis, invasion, and metastasis via the secretion of vascular endothelial growth factor (VEGF), platelet-derived growth factor, and fibroblast growth factor [24]. They promote genome instability and mutation [25].

Vascular endothelial cells

The growth factors that are found in the TME, which are secreted by inflammatory or tumor cells, activate endothelial cells for tumor growth and the formation of new blood vessels. The endothelial cells form the blood vessels' inner layer and are characterized by leakiness, which causes blood, oxygen, drugs, and nutrients not to flow regularly, which in turn causes hypoxia and metastasis [26].

Pericytes

They give structural integrity and support to blood vessels and are represented as a part of the tumor vasculature where they surround endothelial cells. They are negatively correlated with metastasis [27,28]. They have a role in angiogenesis and tumorigenesis through remodeling of the basement membrane, in addition to their phagocytic action [9].

Adipocytes

They are sometimes present in some cancers and produce fuel for cancer cells from fatty acids [29].

Lymphatic endothelial cells

In the case of overexpression of VEGF by macrophages or tumor cells, they can drive lymph-angiogenesis in TME (lymph hyperplasia), which leads to the spread of cancerous cells. They also affect TME remodeling and immune response alteration to the tumor [30].

Immune cells

The innate (macrophages, neutrophils, dendritic cells, innate lymphoid cells, and NK cells) and adaptive (T cells and B cells) immune responses are oriented to recognizing abnormal cells to clean them up. At an early stage of carcinogenesis, antitumor activities are shown by immune cells such as $CD8^+$ T cells, T helper 1 cells, antigen-presenting cells, NK cells, and M1 macrophages, which suppress the growth of tumor. At

the site of inflammation, the immune cells turn into anergy state, which is due to the production of immuno-suppressor cells and inhibitory cytokines [31].

Immune cells include the following.

T lymphocytes

There are different types of T cells according to the tumorigenic state. In the initial state, $CD8^+$ cytotoxic T lymphocytes release interferon gamma, which induces necrosis and apoptosis. The apoptotic residues were removed by phagocytosis. $CD4^+$ T helper 1 and 2 cells secrete cytokines (IL-2 and interferon gamma) and support B-cell response (cytotoxic effect) [13,32]. After the initial state, the immune cells modify and support tumorigenesis, where T regulatory cells (Tregs) exert immunosuppressive roles by producing cytokines such as TGF-β and IL-10, which inhibit the activity of NK, NKT, cells and effective T cells and convert dendritic cells to become immunosuppressive [33,34].

B lymphocytes

They have antitumor activity. They are called tumor-infiltrating B cells because they can infiltrate into microenvironment and differentiate into subtypes. Tumor infiltrating B cells subtypes have a dual effect on tumor, where they inhibit or promote tumor growth, by releasing antibodies and cytokines. They also regulate other types of immune cells such as NK, Tregs, and $CD4^+$ T cells [35,36].

Myeloid-derived suppressor cells

They expand in a variety of cancers. They inhibit $CD8^+$ T cells through the release of nitric oxide synthase. They activate the development of Tregs and macrophage polarization (differentiation) to tumor-associated macrophages (TAMs) [37].

Tumor-associated macrophages

The classically activated macrophages (M1) can recognize pathogens by receptors found on their surface, which activate nuclear factor kappa B (transcription factor) and release pro-inflammatory cytokines such as IL-1β and IL-6 and exhibit antitumor function [38]. TAMs originate from resident macrophages, spleen, or bone marrow by chemokines secreted by endothelial cells, tumor cells, and fibroblasts [39]. They lack their cytotoxic effect, where they induce tumor angiogenesis by secreting VEGF, accumulated in hypoxic and necrotic areas, and release IL-10 and TGF-β to escape from normal immune cells by neutralizing functions of $CD8^+$ T cells and NK cells [40]. They secret epidermal growth factor for tumor growth and are involved in ECM remodeling [41].

Dendritic cells

They are responsible for processing of antigen. Because of the inflammatory and hypoxic state of TME, they cannot stimulate immune system and sometimes inhibit T cells [42].

Neutrophils

They are part of innate immune response, and in the early stage of cancer, they release chemokines that inhibit TGF-β signaling. Later on, they accumulate in tumor and have a promoting effect, enhancing angiogenesis and metastasis by releasing VEGF and matrix-metalloproteinase 9 (MMP-9) [43,44].

Tumor-infiltrating lymphocytes

They are the lymphocytes that can enter and penetrate TME such as T and NK cells, where their accumulation in TME is restricted by CAFs, CAMs, and myeloid-derived suppressor cells. Tumor cells can deal with them by secreting exosomes carrying death factors to kill them via Fas ligand (FasL) (death factor) [45,46].

Extracellular matrix

ECM is a noncellular network. It gives scaffold and structural integrity to the organ and produces a buffering action that keeps homeostasis and water retention. In addition, it mediates different physiological functions, where it binds to growth factors and cell surface receptors (cell adhesion receptors as integrin), which transduce signals to cells that regulate gene transcription for development, wound healing, differentiation, and migration [47,48]. ECM is found as two types: the extracellular basement membrane, which separates epithelial and endothelial cells from stroma, and the interstitial matrix, which forms connective tissue where stromal cells are embedded. Both consists of proteoglycans (PGs) and fibrous proteins. It is mechanically active and always remodeled for development and wound healing, but deregulation of its components leads to cancer progression [49].

PGs are glycosaminoglycans (GAGs) that bind covalently to core protein. GAGs are negatively charged polysaccharide chains composed of N-acetylglucosamine or N-acetylgalactosamine, with monomers of either D-glucuronic or L-iduronic acid. GAGs are either sulfated, such as heparan sulfate, keratan sulfate, and chondroitin sulfate, or

nonsulfated GAGs, such as hyaluronic acid [50,51]. PGs form hydrogel; they can sequester water, which enables them to withstand the stresses exposed to tissues. They store and transmit growth factors. They are also responsible for cell–cell and cell–ECM adhesion and interactions as perlecan, decorin, and syndecan and can recognize binding receptors such as integrin, which is an adhesion receptor responsible for signaling transduction [52]. The main PGs are heparan sulfate proteoglycan (HSPGs), which are present in the cell membrane as syndecan and in the ECM and basement membrane as perlecan [53].

Fibrous proteins are collagen, elastin, fibronectin, laminin, and tenascin. Either tumor cells or their stromal components enhance ECM proteins, where their dysregulation is associated with matrix remodeling, proliferation, invasion, and metastasis. Collagen is the most abundant component of ECM. There are 28 types of collagen with two forms: fibrous, which is found in the interstitial stroma as collagen I, and network, which is found in the basal membrane as collagen VI [47,54]. It is secreted by fibroblasts. It regulates cell–cell adhesion and migration and gives strength to the ECM stroma. Elastin is bound to collagen and gives recoiling and elasticity to tissues. Fibronectin is secreted in dimeric form and has several binding sites to other molecules such as integrin and collagen [55]. It binds cells with ECM and is responsible for cell function, attachment, and migration. Laminin is an important component of the basement membrane. It stabilizes the adhesion of cells by forming a network. It binds with other ECM components and affects cell differentiation and migration. Tenascin affects cell migration and GAGs binding with fibronectin, which induces metastasis [56]. Crosslinking of collagen fibers is through oxidative deamination of lysine residues by lysyl oxidase (LOX), whereas glycation can lead to non-enzymatic collagen crosslinking [31,57].

Role of extracellular matrix remodeling in invasion and metastasis

ECM is in a dynamic state, which means it is always remodeled in normal homeostasis as in wound healing and growth, while the upregulated remodeling, which happens when an imbalance occurs between synthesis and degradation of matrix components, can lead to cancer progression [58]. There are different enzymes that are involved in the remodeling of ECM, which are as follows.

Matrix degrading (remodeling) enzymes

LOX binds collagen I fibers and elastin fibers (which are the most abundant proteins deposited in cancer) to make more rigid fibrils in the matrix, where it becomes stiffer than normal. As collagen expression increased, LOX expression and activity increased, which correlated with poor survival, cell migration, and metastasis. It was reported that more stiffened and remodeled matrix play a key role in tumor progression, angiogenesis, invasiveness, and metastasis [59].

MMPs are produced by CAFs, tumor cells, and infiltrating immune cells. There are 28 types, classified as collagenases (1,8,13), gelatinases (2,9), membrane-type metalloproteinases (14,15,16,17), tissue inhibitor, and other metalloproteinases (19,21,23,27,28). Their overexpression leads to the degradation of ECM and the release of growth factors and cytokines that induce tumor progression. The release of growth factors enhances proliferation and angiogenesis and causes cells to be free in movement to invade vasculature and leads to metastasis [31]. The degradation of the basement membrane helps cancer cells escape and leave its first place (primary tumor). MMP-2 and MMP-9 degrade collagen, fibronectin, gelatin, elastin, and laminin [60]. Membrane type 1 MMP is a cell surface proteinase (secreted on cancer cell surface) that is involved in cancer survival and invasion. It degrades type I collagen and activates MMP-2, which degrades type IV collagen [61].

MMPs are involved in the transition between dormancy state and metastatic growth, where they release antiangiogenic factors such as restin, arrestin, and endostatin, which inhibit angiogenesis and metastasis. They also secrete cytokines such as TGF-β and angiogenic factors such as VEGF and fibroblast growth factor, which activate angiogenesis and metastatic growth. TGF-β activation by MMPs leads to release of collagen 1 and LOX, which in turn leads to ECM remodeling, which causes a suitable media for angiogenesis and metastasis [55].

Heparanase

It is an endoglycosidase enzyme responsible for cleaving of β (1,4)-glycosidic bond between glucosamine residue and glucuronic acid in HSPG chains, which releases shorter chains of heparan sulfate. The degradation of HSPGs leads to the remodeling of ECM, which helps in tumor growth and metastasis by shedding syndecan from the cell surface [62].

Tumor microenvironment, extracellular matrix remodeling, and tumor development and progression

It was found that in normal homeostasis, normal fibroblasts secrete collagen I and III, other fibrous

proteins, and PGs, which form a network within the hydrogel to maintain its normal function. As ECM is highly dynamic and is continually remodeled, when the remodeling is deregulated, it indicates a pathological condition. Degradation enzymes such as MMPs and their inhibition regulators (tissue inhibitor metalloproteinase), heparanase, and LOX regulate the remodeling process [63].

In cancer development, the genetic alterations occurring in tumor cells generate uncontrolled growth, apoptosis resistance, anaerobic glycolysis, and hyperplasia, which cause oxidative stress, acidosis, and hypoxia in TME. DCs, myeloid derived suppressor cells, and TAMs secrete cytokines such as IL-10 and TGF-β, which immunosuppress NK cells and T cells, together with the remodeling of ECM. ECM remodeling is due to the deposition of collagen as a result of response from CAFs and infiltrating immune cells, which in turn leads to angiogenesis that forms the leaky vasculature, which activates invasion and metastasis to a distant place, where after leaving the vasculature, cancer cells with the stromal cells express ECM remodeling enzymes to form a metastatic niche. Cancer cells use ECM to proliferate and expand from micrometastatic to macrometastatic forms [63–65].

Different modalities for treatment of cancer

Surgery, chemotherapy, and radiotherapy alone or combined are the main strategies for cancer therapy worldwide. They are associated with different adverse effects, as drug resistance and destruction of normal cells and the immune system. Targeting therapy has emerged as a challenge for cancer therapy, which aims to target the different proteins and molecules that are involved in cancerous cell division and spread [66,67]. Hormonal therapy is one type of targeted therapy that targets tumors that have estrogen or androgen receptors, but it is limited for a small range of cancers such as breast and prostate cancers [68].

Monoclonal antibodies and inhibitors of tyrosine kinases are considered as developing strategies in targeting therapies. They target cancers that have active antigens and ligands (target proteins) such as breast, lung, kidney, and pancreatic cancers [68]. The mechanism of both of them is as follows.

Monoclonal antibodies work by recognizing a target such as an antigen on cancer cells and using an antibody specific for that target, such as bevacizumab, which targets VEGF-A (the most potent proangiogenic factor) and can reduce angiogenesis. Each monoclonal antibody recognizes a specific protein on the surface of cancer cell. Therefore, different monoclonal antibodies were used for different proteins on the same cancer cell or for different cancer cells where they induce death of cancer cells through blocking the signaling of growth factor receptors and prevent proliferation [69].

Small molecule kinase inhibitors use ligands that target protein kinases such as growth factor receptors, block signals, and inhibit growth. Kinases catalyze protein phosphorylation (the transfer of terminal phosphoryl group from ATP to tyrosine, serine, or therionine amino acid residues) where protein phosphorylation is responsible for the regulation of many cellular processes such as apoptosis, proliferation, migration, and metastasis by switching proteins on. There are 538 human gene-encoded kinases, 37 kinase inhibitors are approved, 150 in clinical phase trials, and many in preclinical trials [70,71].

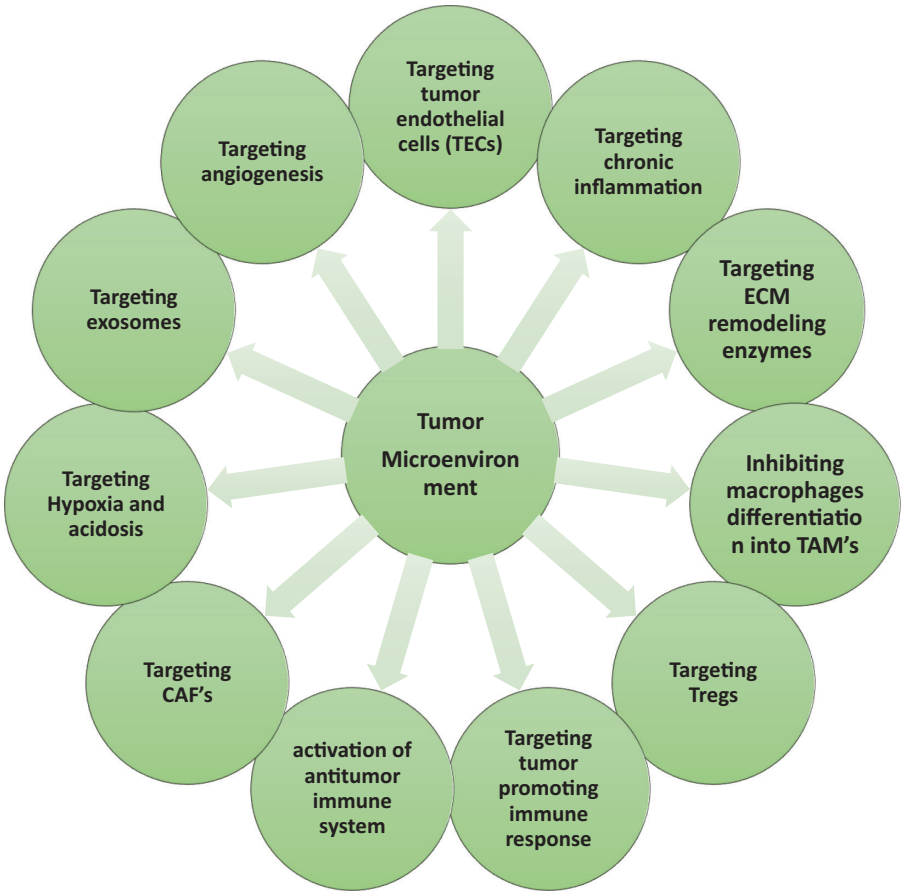
Growth signaling transductions are initiated after binding of growth factors to their receptors on the cell membrane, where a cascade of intracellular molecules are activated and lead to regulation of apoptosis, proliferation, invasion, and metastasis. For that, protein kinase inhibitors can target the receptors with their activated pathways for cancer treatment [72].

Targeting tumor microenvironment components for cancer therapy

As components of TME play a key role in cancer development, targeting one or more components of TME can tackle cancer. A multitargeted therapy that can target cancer cells with its TME can achieve great potential for cancer treatment and management [15,67]. Targeting TME components are shown in Fig. 3.

Targeting ECM remodeling enzymes such as MMPs and heparanase, along with the inhibition of ECM–cell binding receptors, integrin, inhibits the degradation of ECM, which inhibits tumor cell proliferation, migration, and metastasis. The deposition of collagen in ECM due to acidosis, inflammation, tumor cell heterogeneity, and hypoxia results in ECM remodeling, which in turn causes the release of growth signals, inhibits apoptosis, and activates angiogenesis, invasion, and metastasis [73]. For targeting ECM remodeling, the inhibited effect of sulfated polysaccharides on cancer growth and metastasis through inhibition of heparanase enzyme activity was evaluated [74]. In addition, roneparstat as a heparanase inhibitor is also used to inhibit cell growth,

Figure 3



Targeting TME components for cancer therapy. TME, tumor microenvironment.

which is in a phase 1 clinical trial. Other anticancer drugs such as taxol can inhibit single cell migration and doxorubicin can inhibit cluster-type migration. The combination of two drugs can achieve a better anti-metastatic effect [75]. Losartan, which inhibits TGF-β, reduces desmoplasia (collagen release and deposition) and improves chemotherapeutic delivery to cancer cells, which cannot be achieved owing to the stiffness of ECM [76]. Incyclinide inhibits the detachment of tumor cells from ECM, which inhibits metastasis via inhibiting MMPs [65].

Inhibiting macrophages differentiation into TAMs through targeting receptor of colony stimulating factor 1, which is a signal for macrophage differentiation and survival, which can inhibit proliferation, migration, angiogenesis, and metastasis [40]. Another example of TAM depletion is trabectedin, which is an activator of the apoptotic pathway [77].

Targeting Tregs through blocking CD28, which is a stimulator for Treg cells, can inhibit their function and activate tumor suppression. Basiliximab and daclizumab (anti-CD25 antibody and anti-CD25 receptor antibody, respectively) can reduce circulating Tregs expression [40].

Targeting tumor-promoting immune response, besides the activation of antitumor immune system, where the adaptive immune cells such as B and T lymphocytes in TME suppress the immune system by secreting IL-10 and TGF-β, is another option. The innate immune cells as NK cells in TME lead to tumor inhibition by secreting anticancer cytokines such as IL-12 and IL-2 [65]. Blocking tumor promotion can be achieved by using cytokines against immuno-response to anticancer drugs through inhibition of macrophages differentiation into TAMs and inhibition of inflammatory mediators. The anticancer activity of the immune system can be stimulated using cytokines in combination therapies to block inhibition of antibodies production targeting TME [78].

Targeting CAFs (as an anticancer-immunotherapy) is another option. The inflammatory microenvironment

that surrounds tumor (hypoxia, TNF-α, IL-1β, and interferon gamma) causes the release of growth factors such as TGF-β, which stimulate the conversion of resident fibroblasts into CAFs. CAFs stimulate tumor growth and migration of other cells into TME via secretion of ECM components and growth factors. They also stimulate reactive oxygen species production and vice versa, so targeting reactive oxygen species can decrease inflammation [79].The available trials do not have the required effect to target CAFs, and more studies are under investigation [80].

Targeting hypoxia and acidosis is another option. Topotecan and several drugs were used to target hypoxia-inducible factor 1, which was used in clinical trials. In addition, due to Warburg effect, which enables tumor cells to survive in such conditions and suppress immune response, lactic and carbonic acids were accumulated in TME and cause acidification, so using acetazolamide with radiotherapy can target acidification (carbonic anhydrase) and tumor cells [81].

Targeting exosomes

Exosomes are vesicles that are secreted in TME and modulate communication and interaction between cells, which occurs via growth factors, cytokines, and their receptors, where they transfer RNA, proteins, and lipids between cells and modulate the phenotype of recipient cells, which induce CAF transformation, inflammation, and angiogenesis and inhibit immune response [9]. Inhibition of exosome production through targeting pathways that are involved in their production and using them as anticancer drug delivery vehicles can inhibit cancer progression [82].

Targeting angiogenesis via targeting pericytes by antiangiogenic therapies due to their role in angiogenesis is another option. Avastin is an antibody that targets VEGF and inhibits angiogenesis and is approved by FDA [83]. Targeting angiogenesis, invasion, and metastasis by using plant phenol resveratrol [84] and different plant extracts and nano-extracts in hepatocellular carcinoma [85], lung, colon, and breast cancer was carried out [86–88].

Targeting tumor endothelial cells through blocking growth factors that are responsible for their migration and growth, by using gold nanoparticles to inhibit the binding of VEGF with its receptor VEGFR2, which inhibits angiogenesis, is another option [89].

Targeting chronic inflammation by inhibiting cytokines, chemokines, and other stimuli secreted by TAMs that trigger carcinogenesis may inhibit inflammation. For example, phosphomanno-pentose sulfate is used to target inflammatory cells, but it does not affect or modulate the overall survival [90].

Drug delivery and nanotechnology

The development of techniques that enable the delivery of therapeutic agents into cancerous cells with minimal or no effect on normal cells is a great challenge. Using nanotechnology, different obstacles can be overcome such as insufficient amount of drugs, stability and solubility of drugs, nonspecific distribution, poor bioavailability, inability to reach to the appropriate site of action, and inability for early detection or therapeutic response monitoring [91]. The importance of nanoparticle application in cancer treatment for drug delivery is due to their unique properties such as their large surface to mass ratio, increased bioavailability, long circulation time, and their ability to carry, absorb, and bind to other particles (drugs and proteins) [92,93]. In addition, they can surpass different barriers and can increase intracellular delivery, which decreases drug toxicity. Nanoparticles can be divided into two major groups according to their nature: organic and inorganic nanoparticles. Gold nanoparticles are the most prominent inorganic type, which can be easily modified in shape and size with a long circulation half-life, stability, and biocompatibility. Other inorganic nanoparticles such as silica, iron oxide, and silver are also used [94]. The disadvantages of inorganic nanoparticles are their accumulation in the body because of their nonbiodegradable nature. Organic nanoparticles such as liposomes and polymeric nanoparticles have a biodegradable nature, where liposomes can bind with the cell membrane owing to the similarity in their compositions [95]. Liposomes consist of an aqueous core surrounded by two layers of lipid membrane (glycolipid or phospholipid), where hydrophobic molecules can be carried inside the bilayer membrane, whereas hydrophilic particles can be encapsulated within the core. Liposomes are less stable with sterilization difficulty and a short half-life, which can be solved by polyethylene glycol encapsulation. Dendrimers and micelles are polymeric nanoparticles that are composed of biodegradable and biocompatible polymers such as poly lactic acid and poly D-L-lactide-co-glycolic acid, where drugs are either conjugated on their surface or encapsulated inside their polymeric matrix [96]. Poly lactic acid is degraded into lactic acid and poly D-L-lactide-co-glycolic acid is degraded into lactic and

glycolic acid, which are normal substances that are found in the body. Polysaccharides such as pectin, gelatin, and chitosan of natural origin are used as biopolymeric nanoparticles, which are extracted from microorganisms, animals, and plants [97,98]. Their application in nanomedicine is limited owing to their solubility in water and their degradation at high temperatures [99]. Hybrid nanoparticles are those composed of at least two types of nanoparticles such as liposome-polymer or organic and inorganic nanoparticles to improve their properties [100].

Nanoparticles can be designed to bind with different moieties that can target different components in TME, where they can carry combined therapies, which can reduce the probability of multidrug-resistance development [65].

To reach a putative biological target, different strategies can be exploited, such as passive and active drug targeting [101]. Passive targeting depends on the properties of nanoparticles (circulation time, size) and tumor cells (leakiness of blood vessels). Nanoparticle-bound drugs reach to the vasculature that surrounds the tumor, and through leaky vessels (pores through the vessels), which are formed owing to high proliferation rate of cancer cells and hypoxia, they are selectively permeable through the tumor tissue. Besides, with poor lymphatic drainage, which causes retention of nanoparticles, which is called enhanced permeability retention effect, the nanoparticles are accumulated and then the drug is released from them. Active targeting depends on nanoparticle-binding ligands that target certain receptors that are expressed on cancer cells. Monoclonal antibodies can also be used for targeting [53,102].

Once nanoparticles are localized to tumor, they begin their action via one of three mechanisms: free radical-killing mechanism, thermal ablation, or drug release, which can be used in combination or alone to kill cancer cells [102]. Nanotechnology disadvantages include the accumulation and aggregation in the body along with the toxicity of some nanoparticles' nature and the high cost of manufacturing [92].

Some approaches that use nanoparticles are as follows:

(1) Polyethylene glycol attached to gold nanoparticle binding-chemotherapy to protect nanodrug from immune system attack (phagocytosis) [97].
(2) Inserting gold nanoparticle into cancer cells and applying heat (laser) to destroy them [92].
(3) Binding liposome-attached chemotherapy with amino acid to increase protein concentration to accelerate chemotherapy accumulation at tumor where sensors that depend upon nanowires can detect proteins for detection [92].
(4) Binding liposomes with monoclonal antibodies to obtain a less toxic drug and an effective antitumor agent [103].
(5) Radiation therapy can be combined with photodynamic therapy by using luminescent nanoparticles with photosensitizers to kill cancer cells and decrease the radiation dose. The activation of nanoparticles with radiograph generates electrons that destroy cancer cells [104].

Recent directions in cancer therapy

A deep understanding of the interaction between cancer and its microenvironment can predict better therapeutic strategies [105].

Mesenchymal stem cells are loaded with cytotoxic drugs, where they are able to reach to tumor and destroy cancer cells [106].

Green biosynthesis of nanoparticles is done by using natural products, where secondary metabolites act as reducing agents, which is called eco-friendly synthesis [107].

Application of cancer immunotherapy is another approach, which is also called T-cell-mediated therapy because of their ability to attack cancer cells. Immunotherapy is the activation of the immune system to attack cancer cells and kill them, which can be achieved by the following: (a) using cancer treatment vaccines that are prepared from tumor cells, (b) collecting T cells that infiltrate into tumor and treating them with cytokines to be activated, or (c) activation of cells that secrete immune-activating cytokines such as IL-12, TNF, and IL-2 [68,108].

Pretreatment such as photodynamic therapy, hyperthermia, and radiation therapy should be used in combination with nanomedicines due to the highly changeable TME components to increase their target achievement [109].

Combination therapies using more than one therapy with different mechanisms of action to overcome drug resistance [110,111] with improvement of nanocarriers for drug delivery application to overcome obstacles of poor solubility and low permeability are another option [112].

Using a combination of nanodrug delivery systems and cancer immunotherapy is another option [68].

Conclusion

Cancer cannot be considered as a state of uncontrolled cell growth because it is also a dysregulation of its microenvironment.

About 30% of cancer deaths can be avoided by improving human lifestyle.

Advances in understanding the contribution of TME and ECM in cancer progression lead to the discovery of promising therapies that can prevent proliferation, invasion, and metastasis, which provide hope for cancer treatment.

Targeting TME components or the mediators of their interaction and communication can give a complementary treatment option.

Nanotechnology plays a key role in cancer diagnosis and treatment.

Some nanomaterials are toxic in nature or become toxic under certain conditions, which should be taken into consideration in designing of nanoparticle drug.

Acknowledgements

The author has made the conception or design of the work or the acquisition, analysis, or interpretation of data. The manuscript had been revised critically for important intellectual content and final approval of the version to be published.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1 World Health Organization fact sheet, cancer, 2022.

2 Ibrahim AS, Khaled HM, Mikhail NNH, Baraka H, Kamel K. Cancer incidence in Egypt: results of the national population-based cancer registry program. J Cancer Epidemol 2014; 2014:437971.

3 World Health Organization /Agency for Research on Cancer; Egypt. Fact sheet, 2021.

4 Lopez-Lazaro M. What is the main cause of cancer? Cancer Stud Therap J 2016; 1:1–2.

5 Lewandowska AM, Rudzki M, Rudzki S, Lewandowski T, Laskowska B. Environmental risk factors for cancer – review paper. Ann Agri Environ Med 2019; 26:1–7.

6 Fouad YA, Aanei C. Revisiting the hallmarks of cancer. Am J Cancer Res 2017; 7:1016–1036.

7 Cao L, Zhu Y, Wang W, Wang G, Zhang S. Emerging nano-based strategies against drug resistance in tumor chemotherapy. Front Bioengin Biotech 2021; 9:798882.

8 Hinshaw DC, Shevde LA. The tumor microenvironment innately modulates cancer progression. Cancer Res 2019; 79:4557–4567.

9 Baghban R, Roshangar L, Jahanban-Esfahlan R. Tumor microenvironment complexity and therapeutic implications at a glance. Cell Commun Signal 2020; 18:59–78.

10 Paget S. The distribution of secondary growths in cancer of the breast. Cancer Metastasis Rev 1989; 8:98–101.

11 Ribatti D, Mangialardi G, Vacca A. Stephen Paget and the 'seed and soil' theory of metastatic dissemination. Clin Exp Med 2006; 6:145–149.

12 Chen F, Zhuang X, Lin L, Yu P, Wang Y, Shi Y, *et al.* New horizons in tumor microenvironment biology: challenges and opportunities. BMC Med 2015; 13:1–13.

13 Joyce JA, Fearon DT. T cell exclusion, immune privilege, and the tumor microenvironment. Science 2015; 348:74–80.

14 Colotta F, Allavena P, Sica A, Garlanda C, Mantovani A. Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. Carcinogen 2009; 30:1073–1081.

15 Tsai MJ, Chang WA, Huang MS, Kuo PL. Tumor microenvironment: a new treatment target for cancer. ISRN Biochem 2014; 2014:351959.

16 Gao F, Liang B, Reddy ST, Farias-Eisner R, Su XL. Role of inflammation-associated microenvironment in tumorigenesis and metastasis. Curr Cancer Drug Targets 2014; 41:30–45.

17 Jayappa KD, Kovi RC, Chatterjee S. Interplay between tumor microenvironment and cancer cells. Bio Med Res Inter 2016; 2016:4650498.

18 Tao J, Yang G, Zhou W, Qiu J, Chen G, Luo W, *et al.* Targeting hypoxic tumor microenvironment in pancreatic cancer. J Hematol Oncol 2021; 14:1–25.

19 Liu T, Han C, Wang S, Fang P, Ma Z, Xu L, *et al.* Cancer-associated fibroblasts: an emerging target of anti-cancer immunotherapy. J Hematol Oncol 2019; 12:86–101.

20 Marsh T, Pietras K, McAllister SS. Fibroblasts as architects of cancer pathogenesis. Biochim Biophys Acta 2012; 1832:1070–1078.

21 Erez N, Truitt M, Olson P, Arron ST, Hanahan D. Cancer-associated fibroblasts are activated in incipient neoplasia to orchestrate tumor promoting inflammation in an NF-kappa B-dependent manner. Cancer Cell 2010; 17:135–147.

22 Bartoschek M, Oskolkov N, Bocci M, Lövrot J, Larsson C, Sommarin M, *et al.* Spatially and functionally distinct subclasses of breast cancer-associated fibroblasts revealed by single cell RNA sequencing. Nat Commun 2018; 9:5150–5163.

23 Douglas H, Coussens LM. Accessories to the crime: functions of cells recruited to the tumor microenvironment. Cancer Cell 2012; 21:309–22.

24 Spaeth EL, Dembinski JL, Sasser AK, Watson K, Klopp A, Hall B, *et al.* Mesenchymal stem cell transition to tumor associated fibroblasts contributes to fibrovascular network expansion and tumor progression. PLoS ONE 2009; 4:e4992.

25 Wei R, Liu S, Zhang S, Min L, Zhu S. Cellular and extracellular components in tumor microenvironment and their application in early diagnosis of cancers. Anal Cellul Pathol 2020; 2020:6283796.

26 Hida K, Maishi N, Annan DA, Hida Y. Contribution of tumor endothelial cells in cancer progression. Int J Mol Sci 2018; 19:1272–1284.

27 Armulik A, Genové G, Betsholtz C. Pericytes: developmental, physiological, and pathological perspectives, problems, and promises. Dev Cell 2011; 21:193–215.

28 Cooke VG, LeBleu VS, Keskin D, Khan Z, O'Connell JT, Teng Y, *et al.* Pericyte depletion results in hypoxia-associated epithelial-to-mesenchymal transition and metastasis mediated by met signaling pathway. Cancer Cell 2012; 21:66–81.

29 Nieman KM, Kenny HA, Penicka CV, Ladanyi A, Buell-Gutbrod R, Zillhardt MR, *et al.* Adipocytes promote ovarian cancer metastasis and provide energy for rapid tumor growth. Nat Med 2011; 17:1498–1503.

30 Swartz MA, Lund AW. Lymphatic and interstitial flow in the tumor microenvironment: linking mechanobiology with immunity. Nat Rev Cancer 2012; 12:210–219.

31 Cox TR, Erler JT. Remodeling and homeostasis of the extracellular matrix: implications for fibrotic diseases and cancer. Dis Model Mech 2011; 4:165–178.

32 Castro F, Cardoso AP, Gonçalves RM, Serre K, Oliveira MJ. Interferon-gamma at the crossroads of tumor immune surveillance or evasion. Front Immunol 2018; 9:1–12.

33 Campbell DJ, Koch MA. Treg cells: patrolling a dangerous neighborhood. Nat Med 2011; 7:929–930.

34 Balkwill FR, Capasso M, Hagemann T. The tumor microenvironment at a glance. J Cell Sci 2012; 125:5591–5596.

35 Martin F, Chan AC. B cell immunobiology in disease: evolving concepts from the clinic. Ann Rev Immunol 2006; 24:467–496.

36 Guo FF, Cui JW. The role of tumor-infiltrating B cells in tumor immunity. J Oncol 2019; 2019:2592419.

37 Alberto M, Paola A, Antonio S, Frances B. Cancer-related inflammation. Nature 2008; 454:436–444.

38 Mantovani A, Sica A, Sozzani S, Allavena P, Vecchi A, Locati M. The chemokine system in diverse forms of macrophage activation and polarization. Trends Immunol 2004; 25:677–686.

39 Zhu Y, Herndon JM, Sojka DK, Kim K-W., Knolhoff BL, Zuo C, *et al.* Tissue-resident macrophages in pancreatic ductal adenocarcinoma originate from embryonic hematopoiesis and promote tumor progression. Immunity 2017; 47:323–38.

40 Laplagne C, Domagala M, Le Naour A, Quemerais C, Hamel D, Fournie J-J, *et al.* Latest advances in targeting the tumor microenvironment for tumor suppression. Int J Mol Sci 2019; 20:4719–4753.

41 Murray PJ, Allen JE, Biswas SK, Fisher EA, Gilroy DW, Goerdt S, *et al.* Macrophage activation and polarization: nomenclature and experimental guidelines. Immunity 2014; 41:14–20.

42 Gabrilovich DI, Ostrand-Rosenberg S, Bronte V. Coordinated regulation of myeloid cells by tumours. Nat Rev Immunol 2012; 12:253–268.

43 Casbon A-J., Reynaud D, Park C, Khuc E, Gan DD, Schepers K, *et al.* Invasive breast cancer reprograms early myeloid differentiation in the bone marrow to generate immunosuppressive neutrophils. Proc Natl Acad Sci USA 2015; 112:E566– E575.

44 Shrihari TG. Endorphins on cancer: a novel therapeutic approach. J Carcinog Mutagen 2017; 8:298–300.

45 Valenti R, Huber V, Iero M, Filipazzi P, Parmiani G, Rivoltini L. Tumor-released microvesicles as vehicles of immunosuppression. Cancer Res 2007; 67:2912–2915.

46 Fridman WH, Page's F, Saute's-Fridman C, Galon J. The immune contexture in human tumours: impact on clinical outcome. Nat Rev Cancer 2012; 12:298–306.

47 Frantz C, Stewart KM, Weaver VM. The extracellular matrix at a glance. J Cell Sci 2010; 123:4195–4200.

48 Theocharis AD, Skandalis SS, Gialeli C, Karamanos NK. Extracellular matrix structure. Adv Drug Deliv Rev 2016; 97:4–27.

49 Yue B. Biology of the extracellular matrix: an overview. J Glaucoma 2014; 23:S20–S23.

50 Schaefer L, Schaefer RM. Proteoglycans: from structural compounds to signaling molecules. Cell Tissue Res 2010; 339:237–246.

51 Walimbe T, Panitch A. Proteoglycans in biomedicine. Resurgence of an underexploited class of ECM molecules. Front Pharmacol 2020; 10:1–13.

52 Harisi R, Dudás J, Timár F, Pogany G, Timár J, Kovalszky I, *et al.* Invasive growth and topoisomerase-switch induced by tumorous extracellular matrix in osteosarcoma cell culture. Cell Biol Int 2005; 29:959–967.

53 Harisi R, Dudas J, Nagy-Olah J, Timar F, Szendroi M, Jeney A. Extracellular matrix induces doxorubicin-resistance in human osteosarcoma cells by suppression of p53 function. Cancer Biol Ther 2007; 6:1240–1246.

54 Gordan MK, Hahn RA. Collagens. Cell Tissue Res 2010; 339:247–257.

55 Kular JK, Basu S, Sharma RI. The extracellular matrix: structure, composition, age-related differences, tools for analysis and applications for tissue engineering. J Tissue Eng 2014; 5:1–17.

56 Pal S, Moulik S, Dutta A, Chatterjee A. Extracellular matrix protein laminin induces matrix metalloproteinase-9 in human breast cancer cell line mcf-7. Cancer Microenviron 2014; 7:71–78.

57 Yamauchi M, Sricholpech M. Lysine post-translational modifications of collagen. Essays Biochem 2012; 52:113–133.

58 Walker C, Mojares E, Hernández ADR. Role of extracellular matrix in development and cancer progression. Int J Mol Sci 2018; 9:3028–3059.

59 Erler JT, Bennewith KL, Cox TR, Lang G, Bird D, Koong A, *et al.* Hypoxia-induced lysyl oxidase is a critical mediator of bone marrow cell recruitment to form the pre-metastatic niche. Cancer Cell 2009; 15:35–44.

60 Gaggiano C, Vitale A, Obici L, Merlini G. Clinical features at onest and genetic characterization of pediatric and adult patients with TNF-α receptor-associated periodic syndrome (TRAPS): a series of 80 cases from the AIDA network. Mediat Inflamm 2020; 2020:ID 8562485.

61 Seiki M. Membrane-type 1 matrix metalloproteinase: a key enzyme for tumor invasion. Cancer Lett 2003; 194:1–11.

62 Masola V, Bellin G, Gambaro G, Onisto M. Heparanase: a multitasking protein involved in extracellular matrix (ECM) remodeling and intracellular events. Cells 2018; 7:236–247.

63 Altinay S. Is extracellular matrix a castle against to invasion of cancer cells? In: Xu K, (editor.). Tumor metastasis. China: Intech Open. 2016. 23–42

64 Chen F, Chen J, Yang L, Liu J, Zhang X, Tu Q, *et al.* Extracellular vesicle-packaged HIF-1α-stabilizing lncRNA from tumor-associated macrophages regulates aerobic glycolysis of breast cancer cells. Nat Cell Biol 2019; 21:498–510.

65 Rodrigues CR, Mendes R, Baptista PV, Fernandes AR. Cancer therapy. Int J Mol Sci 2019; 20:840–871.

66 Nounou MI, El Amrawy F, Ahmed N, Abdelraouf K, Goda S, Syed-Sha-Qhattal H. Breast cancer: conventional diagnosis and treatment modalities and recent patents and technologies. Breast Cancer (Auckl) 2015; 9(S2):17–34.

67 Yuan Y, Ng YCJ, Sun CK, Chen QNM. Role of the tumor microenvironment in tumor progression and the clinical applications (review). Oncol Rep 2016; 35:2499–2515.

68 Kim K, Khang D. Past, present and future of anticancer. Nanomedicine 2020; 15:5719–5743.

69 Zahavi D, Weiner L. Monoclonal antibodies in cancer therapy. Antibodies 2020; 9:34–54.

70 Chahrour O, Cairns D, Omran Z. Small molecule kinase inhibitors as anti-cancer therapeutics. MiniRev Med Chem 2012; 12:399–411.

71 Bhullar KS, Lagarón NO, McGowan EM, Parmar I, Jha A, Hubbard BP, *et al.* Kinase-targeted cancer therapies: progress, challenges and future directions. Mol Cancer 2018; 17:48–68.

72 Ott PA, Adams S. Small-molecule protein kinase inhibitors and their effects on the immune system: implications for cancer treatment. Immunotherapy 2011; 3:213–227.

73 Pickup MW, Mouw JK, Weaver VM. The extracellular matrix modulates the hallmarks of cancer. EMBO Rep 2014; 15:1243–1253.

74 Ali MM, Abdel-Halim AH, Mahmoud AE, Abd El-Kader MA, Soliman SM. Anticancer, antiangiogenesis and antimetastasis properties of prepared sulfated oligosaccharides on chemically induced hepatocellular carcinoma in rats. Der Pharma Chem 2014; 6:354–366.

75 Harisi R, Kenessey I, Olah JN, Timar F, Babo I, Pogany G, *et al.* Differential inhibition of single and cluster type tumor cell migration. Anticancer Res 2009; 29:2981–2985.

76 Coulson R, Liew SH, Connelly AA, Yee NS, Deb S, Kumar B, *et al.* The angiotensin receptor blocker, Losartan, inhibits mammary tumor development and progression to invasive carcinoma. Oncotarget 2017; 8:18640–18656.

77 Liguori M, Buracchi C, Pasqualini F, Bergomas F, Pesce S, Sironi M, *et al.* Functional TRAIL receptors in monocytes and tumor-associated macrophages: A possible targeting pathway in the tumor microenvironment. Oncotarget 2016; 7:41662–41676.

78 Waldmann TA. Cytokines in cancer immunotherapy. Cold Spring Harb Perspect Biol 2018; 10:a028472.

79 Haider M, Elsherbeny A, Pittalà V, Consoli V, Alghamdi MA, Hussain Z, *et al.* Nanomedicine strategies for management of drug resistance in lung cancer. Int J Mol Sci 2022; 23:1853–1882.

80 Kobayashi H, Enomoto A, Woods SL, Burt AD, Takahashi M, Worthley DL. Cancer-associated fibroblasts in gastrointestinal cancer. Nat Rev Gastroenterol Hepatol 2019; 16:282–295.

81 Kolosenko I, Avnet S, Baldini N, Viklund J, De Milito A. Therapeutic implications of tumor interstitial acidification. Semin Cancer Biol 2017; 43:119–133.

82 Bastos N, Ruivo CF, da Silva S, Melo SA. Exosomes in cancer: use them or target them? Semin Cell Dev Biol 2018; 78:13–21.

83 Fukumura D, Jain RK. Tumor microenvironment abnormalities: causes, consequences, and strategies to normalize. J Cell Biochem 2007; 101:937–949.

84 Abdel-Halim AH, Fyiad AA, Ali MM, Soliman SM. Anticancer properties of resveratrol on chemically induced hepatocellular carcinoma in rats:

inhibition of metastasis and angiogenesis. J Chem Pharma Res 2015; 7:913–921.

85 Ali MM, Borai IH, Ghanem HM, Abdel-Halim AH, Mousa FM. The prophylactic and therapeutic effects of *Momordica charantia* methanol extract through controlling different hallmarks of the hepatocarcinogenesis. Biomed Pharma 2018; 98:491–498.

86 Hassan SK, Mousa AM, El-Sammad NM, Abdel-Halim AH, Khalil WKB, Elsayed EA, *et al.* Antitumor activity of *Cuphea ignea* extract against benzo(a)pyrene-induced lung tumorigenesis in Swiss Albino mice. Toxicol Rep 2019; 6:1071–1085.

87 Aboulthana WM, Ibrahim NE, Osman NM, Seif MM, Hassan AK, Youssef AM, *et al.* Evaluation of the biological efficiency of silver nanoparticles biosynthesized using *Croton tiglium* L. seeds extract against azoxymethane induced colon cancer in rats. Asian Pac J Cancer Prev 2020; 21:1369–1389.

88 Abdel-Halim AH, Fyiad AA, Aboulthana WM, Youssef AM, Sabry NM, Khalil WKB, *et al.* Evaluation of the therapeutic effect of nano-gold *Bauhinea-variegata* leaves extract against breast cancer-induced rats. Int J Pharm Res 2021; 10:077–091.

89 Zhang Y, Xiong X, Huai Y, Dey A, Hossen MN, Roy RV, *et al.* Gold nanoparticles disrupt tumor microenvironment – endothelial cell cross talk to inhibit angiogenic phenotypes in vitro. Bioconjug Chem 2019; 30:1724–1733.

90 Meirovitz A, Goldberg R, Binder A, Rubinstein AM, Hermano E, Elkin M. Heparanase in inflammation and inflammation-associated cancer. F FEBS.J. 2013; 280:2307–2319.

91 Hassan T, Huang X, Zhou C, Khan MSG, Saeed S. Nanoparticles in cancer treatment: a narrative review. Life Environ Sci 2021; 58:33–50.

92 Haque N, Khalel RR, Parvez N, Yadav S, Hwisa N, Al-Sharif MS, *et al.* Nanotechnology in cancer therapy: a review. Chem Pharm Res 2010; 2:161–168.

93 Leong DT, Ng KW. Probing the relevance of 3D cancer models in nanomedicine research. Adv Drug Deliv Rev 2014; 79–80:95–106.

94 Taylor A, Wilson KM, Murray P, Fering DG, Levy R. Long-term tracking of cells using inorganic nanoparticles as contrast agents: are we there yet? Chem Soc Rev 2012; 41:2707–2717.

95 Kummerer K, Menz J, Schubert T, Thielemans W. Biodegradability of organic nanoparticles in the aqueous environment. Chemosphere 2011; 82:1387–1392.

96 Amoabediny G, Haghiralsadat F, Naderinezhad S, Helder MN, Kharanaghi EA, Arough JM. Overview of preparation methods of polymeric and lipid-based (niosome, solid lipid, liposome) nanoparticles: a comprehensive review. Int J Polym Mater Polym Biomater 2017; 67:383–400.

97 Mahapatro A, Singh DK. Biodegradable nanoparticles are excellent vehicle for site directed in-vitru delivery of drugs and vaccines. J Nano Biotech 2011; 9:55–66.

98 Massironi A, Morelli A, Puppi D, Chiellini F. Renewable polysaccharides micro/nanostructures for food and cosmetic applications. Molecules 2020; 25:4886–4891.

99 Patra JK, Das G, Fraceto LF, Campos EVR, Rodriguez-Torres MP, Acosta-Torres LS, *et al.* Nano based drug delivery systems: recent developments and future prospects. J Nanotech 2018; 16:71–104.

100 Soares DCF, Domingues SC, Viana DB, Tebaldi ML. Polymer-hybrid nanoparticles: current advances in biomedical applications. Biomed Pharmacoth 2020; 131:110695.

101 Lammers T, Kiessling F, Hennink WE, Storm G. Drug targeting to tumors: principles, pitfalls and (pre-) clinical progress. J Control Release 2012; 161:175–187.

102 Gmeiner WH, Ghosh S. Nanotechnology for cancer treatment. Nanotechnol Rev 2015; 3:111–122.

103 Aliosmanoglu A, Basaran I. Nanotechnology in cancer treatment. J Nanomed Biotherapeut Discov 2012; 2:107–110.

104 Xu J, Gao J, Wei Q. Combination of photodynamic therapy with radiotherapy for cancer treatment. J Nanomater 2016; 2016:8507924.

105 de Looff M, de Jong S, Kruyt FAE. Multiple interactions between cancer cells and the tumor microenvironment modulate TRAIL signaling: implications for TRAIL receptor targeted therapy. Front Immunol 2019; 10:1530–1545.

106 Wu HH, Zhou Y, Tabata Y, Gao JQ. Mesenchymal stem cell-based drug delivery strategy: from cells to biomimetic. J Control Release 2019; 294:102–113.

107 Aritonang HF, Koleangan H, Wuntu AD. Synthesis of silver nanoparticles using aqueous extract of medicinal plants' (*Impatiens balsamina* and *Lantana camara*) fresh leaves and analysis of antimicrobial activity. Int J Microbiol 2019; 2019:8642303.

108 Sebastian R. Nanomedicine – the future of cancer treatment: a review. J Cancer Prev Cuu Res 2017; 8:1–6.

109 Overchuk M, Zheng G. Overcoming obstacles in the tumor microenvironment: recent advancements in nanoparticle delivery for cancer theranostics. Biomaterials 2018; 156:217–237.

110 Swain S, Sahu PK, Beg S, Babu SM. Nanoparticles for cancer targeting: current and future directions. Curr Drug Deliv 2016; 13:1290–1302.

111 Galal SA, Khairat SHM, Ali HI, Shouman SA, Attia YM, Ali MM, *et al.* Part II: new candidates of pyrazole-benzimidazole conjugates as checkpoint kinase 2 (Chk2) inhibitors. Eur J Med Chem 2018; 144:859–873.

112 Elzoghby AO, El-Lakany SA, Helmy MW, Abu-Serie, Elgindy NA. Shell-crosslinked zein nanocapsules for oral codelivery of exemestane and resveratrol in breast cancer therapy. Nanomedicine 2017; 12:2785–2805.