REVIEW

Nanomedicines: intervention in inflammatory pathways of cancer

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Abstract

Inflammation is a complex defense process that maintains tissue homeostasis. However, this complex cascade, if lasts long, may contribute to pathogenesis of several diseases. Chronic inflammation has been exhaustively studied in the last few decades, for its contribution in development and progression of cancer. The intrinsic limitations of conventional anti-inflammatory and anti-cancer therapies triggered the development of nanomedicines for more effective and safer therapies. Targeting inflammation and tumor cells by nanoparticles, encapsulated with active therapeutic agents, offers a promising outcome with patient survival. Considerable technological success has been achieved in this field through exploitation of tumor microenvironment, and recognition of molecules overexpressed on endothelial cells or macrophages, through enhanced vascular permeability, or by rendering biomimetic approach to nanoparticles. This review focusses on the inflammatory pathways in progression of a tumor, and advancement in nanotechnologies targeting these pathways. We also aim to identify the gaps that hinder the successful clinical translation of nanotherapeutics with further clinical studies that will allow oncologist to precisely identify the patients who may be benefited from nanotherapy at time when promotion or progression of tumor initiates. It is postulated that the nanomedicines, in near future, will shift the paradigm of cancer treatment and improve patient survival.

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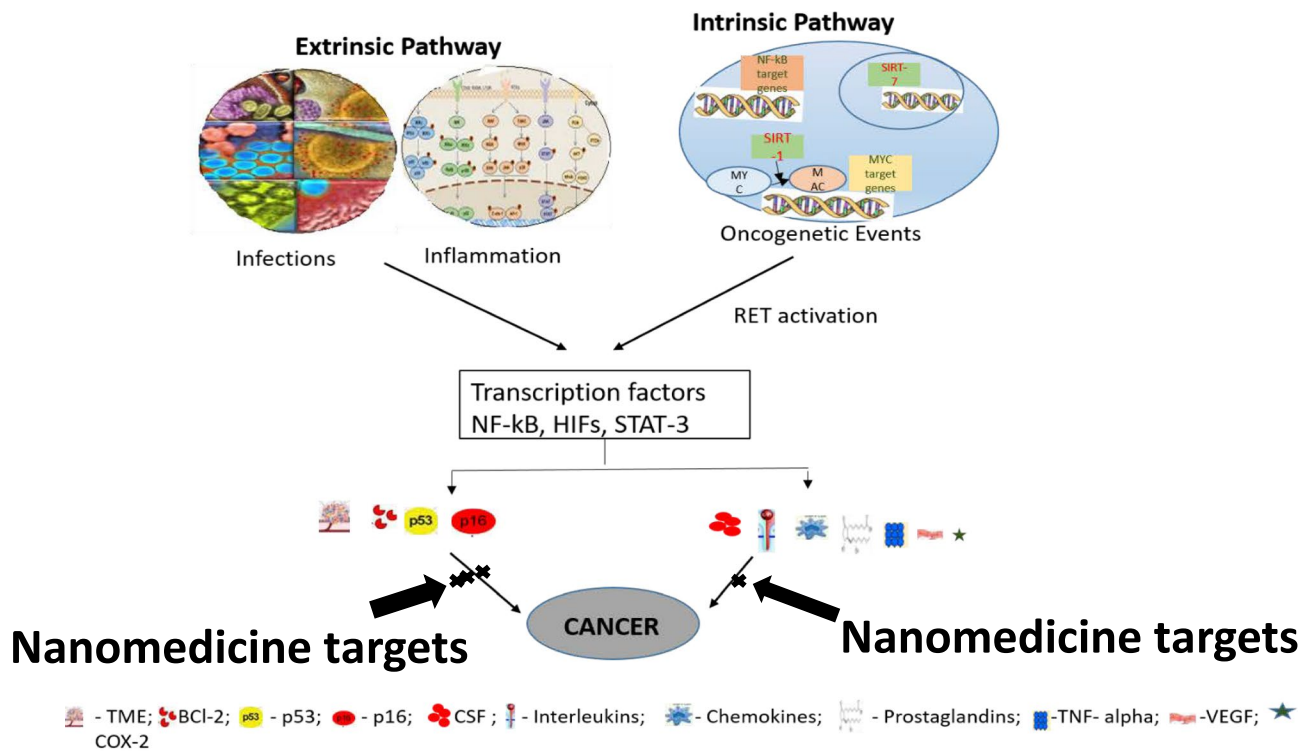   Abdulaziz University, Jeddah 21589, Saudi Arabia

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Graphical abstract

Extrinsic Pathway

Infections   Inflammation

Intrinsic Pathway

Oncogenetic Events

RET activation

Transcription factors
NF-kB, HIFs, STAT-3

CANCER

Nanomedicine targets   **Nanomedicine targets**

- TME; - BCl-2; p53 - p53; - p16; - CSF; - Interleukins; - Chemokines; - Prostaglandins; -TNF- alpha; -VEGF; COX-2

Keywords Nanoparticles · Nanotechnology · Inflammation · Tumor microenvironment · Enhanced permeability and retention (EPR) · Passive targeting · Active targeting

Abbreviations

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(si)-RNA	Small interfering RNA
bFGF	Basic fibroblast growth factors
COX-2	Cyclo-oxygenase
CSF	Colony stimulating factors
EGFR	Epidermal growth factor receptor
EPR	Enhanced permeability and retention
IL	Interleukin
NMs	Nanomedicines
NPs	Nanoparticles
PTC	Papillary thyroid carcinoma
TME	Tumor microenvironment
VEGF	Vascular endothelial growth factors
NIDDM	Non-insulin-dependent diabetes
ICAM	Intercellular adhesion receptor
VCAM	Vascular cell adhesion molecule
MMP9	Matrix metallopeptidase-9
NSAIDs	Non-steroidal anti-inflammatory drugs
TNF-α	Tumor necrosis factor alpha
RET	Rearranged transfection
NF-κB	Nuclear factor-κB
IBD	Inflammatory bowel disease
APC	Antigen presenting cell
MMR	Mismatch repair
CIMP	CpG island methylation pathway
MAPK	Mitogen-activated protein kinase
CMS	Consensus molecular subtype
TGF-β	Transforming growth factor-β
Th	T helper
Ig	Immunoglobulin
PGE	Prostaglandins
DNMT	DNA methyltransferases
TNBC	Triple-negative breast cancer

Introduction

Pathogenic micro-organisms, free radicals, metabolic processes, physical and biological stresses and several other factors initiate a mechanism of defense by the body which is termed as inflammation (Li et al. 2017b). This process of defense, however, if lasts for a long period of time, may

become detrimental to the tissues, which in turn, may contribute to the pathogenesis of chronic disorders (Cronkite and Strutt 2018). Arthritis, asthma, acute respiratory distress syndrome, non-insulin dependent diabetes (NIDDM), obesity, cardiovascular disorders, Crohn's disease, Bowel syndrome, COVID-19, neurodegenerative diseases and cancer are just a few examples with altered homeostasis(Wang et al. 2021a).

Chronic inflammation follows a cascade of complex processes. However, advancement in understanding its mechanism at cellular and molecular levels, has tried to unloop its pathophysiological mechanisms (Antonelli and Kushner 2017, Medzhitov 2010). During the last few decades, the contribution of inflammation and immune system in the development and progression of cancer has been enormously studied (Karin Karin 2020). A number of proteins including Intercellular Adhesion Receptor (ICAM), Vascular Cell Adhesion Molecule (VCAM), Selectins, etc. are expressed by the cells involved in inflammation (Zhao et al. 2021). Additionally, enhanced permeability and retention (EPR) effect interferes with vascular integrity of the inflamed tissues and gives rise to neovascularization. Hypoxia and inflammation are the critical factors for neo-angiogenesis. Hypoxia activates inducible transcription factors like HIF-1 and HIF-2 as well as growth factors like vascular endothelial growth factors (VEGF) and basic fibroblast growth factors (bFGF) (Brusini et al. 2020). Inflammation aids

the proliferation and prolongs survival of malignant cells, facilitate angiogenesis, metastasis, affect immune responses and reduce the response to chemotherapy (Mantovani et al. 2008).

Tumor microenvironment (TME) is a complex network of cells containing fibroblasts and vascular cells (together called stromal cells) and inflammatory immune cells. Neovascularization, with rapid endothelial proliferation, takes place to meet the metabolic demands of rapidly multiplying cancer cells. The vascular structure so formed, has an aberrant 'leaking' architecture with an undefined morphology of venules, capillaries and arterioles (Fig. 1), which may influence the extravasation of NPs to the tumor cells (Deli 2009). However, the specific contribution of tumor neo-vasculature to the permeability of nano-molecules remains poorly understood. It has been established that tumor-related chronic inflammation has a significant impact on TME (Ma et al. 2013). Not only inflammatory mediators, but also, cationic polymers and other tight junction modulators interact with endothelium and cause endothelial contraction and disassemble the tight junctions. It further induces vascular leakiness, which aids the delivery of NPs (with an adequate circulation half-life) to the tumors. Chronic inflammation, thus, influences not only the composition of TME, but also affects the plasticity of cancerous and stromal cells. Researchers have successfully exploited the EPR to deliver the drugs encapsulated in NPs through this leaky vasculature (Vasan
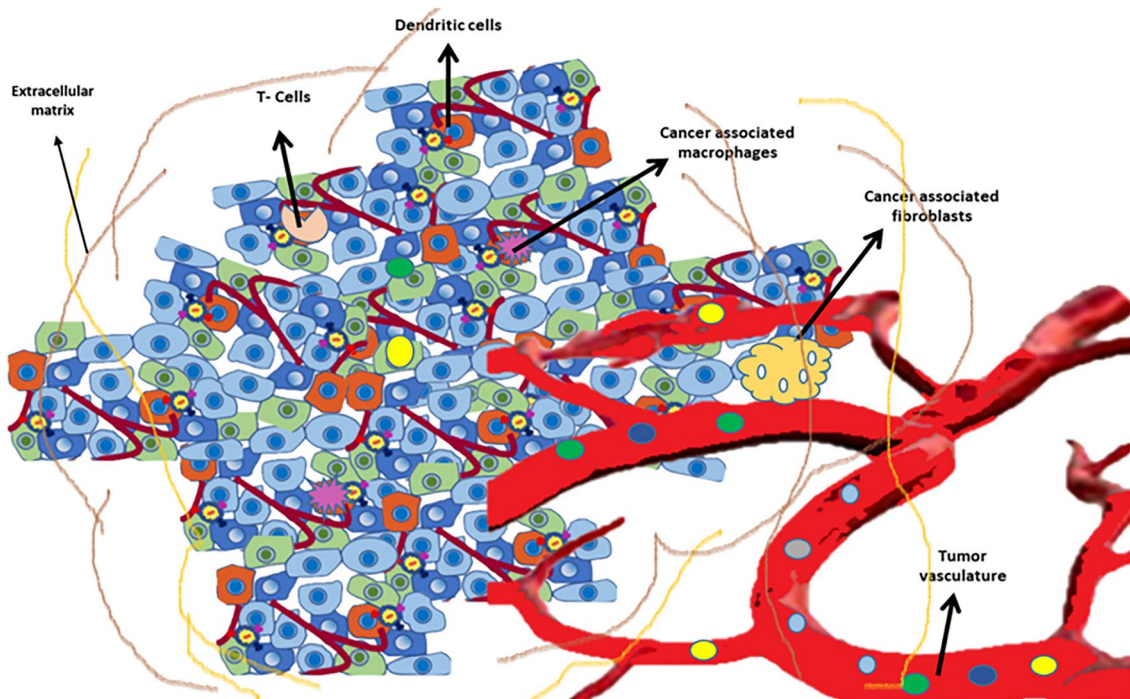
Fig. 1 Tumor micro-environment with inflammatory associated cells and vascularization: therapeutic drugs strategy involves intervention of Nanomedicine to block these cells producing inflammatory mediators

et al. 2019). Nevertheless, this advanced approach of drug delivery can influence NPs and protein interaction, systemic circulation, tumor tissue penetration, tumor-cell internalization and perivascular TME (Crusz and Balkwill 2015).

Vascular permeability, on the other hand, in acute inflammation is enhanced by neutrophils, which release neutrophil elastase, myeloperoxidase and matrix metallopeptidase-9 (MMP9). Medical scientists have gained success in manipulating this leaky inflammatory vasculature to deliver the drugs as nanoparticles/liposomes in experimental rats with neuro-inflammatory disorders (Cavaletti et al. 2009). Conventional treatment options for inflammatory diseases were mainly steroids and non-steroidal anti-inflammatory drugs NSAIDs. Novel therapeutic strategies include leukotriene inhibitors, cytokine inhibitors, Tumor Necrosis Factor Alpha (TNF-α) inhibitors and interleukin-1 monoclonal antibodies inhibitors which ameliorate the inflammatory process(Farzaei et al. 2019). Although these strategies target the inflammatory mediators, nevertheless, an optimal pharmacological outcome is not achieved due to non-specific distribution, low bioavailability, short half-life and/or possible severe adverse effects associated with these drugs. Further high dosages and prolonged treatment may cause off-target effects along with the patient non-compliance (Hang et al. 2021). The limited therapeutic effect of these drugs laid the necessity for a more sustained drug response, which can only be achieved by a more comprehensive approach that can target the critical points of signal transduction pathways involved in the cascade of an inflammatory process.

Nanoplatforms: basic and roles in cancer therapy

The advancement is nanoscience has opened multiple avenues in therapeutics of cancer in addition to existing protocols. The use of nanotechnology has not only helped early detection or diagnosis of cancer but also reduced the mortality rate among such patients with nanomedicines (Khan and Khan 2020). Target drug delivery of nanomedicines is able to reduce the toxicity along with proper compartment distribution and accumulation at the site of tumors. The drugs in nano-forms have various carrier molecules to exert their therapeutic effects of active chemical constituent and can be altered by change in chemo-physio on optical properties depending upon the conditions of patients (Khan 2020). Further recent advances in understanding the underlying immunopathology of inflammation in cancer has led to the development of a novel concept of drug delivery via nanoparticles and liposomes. These are the tiny drug carriers, made up of synthetic or natural materials, ranging from a few tenths to hundredths nanometer in size (Agrahari et al. 2019).This review focus on the inflammatory pathways in progression

of a tumor, and nanomedicines as a novel concept of drug delivery in the management of cancer. While some of these nanomaterial's act as a drug carrier, at the same time, others may themselves possess a therapeutic potential. We also aim to identify the gaps and reveal the hindrances that come across the cancer nano-therapies in prolonging patient survival, and to close the loop of our current understanding of tumor biology and interactions between NPs and biological system, which are critical to maximize the impact of therapy.

Inflammatory pathways in cancer

Accumulating evidence illustrate that chronic inflammation predisposes the increased risk of cancer. In certain types of cancer, an inflammatory microenvironment is present before malignant changes take place. Conversely, oncogenic genes in other types may produce an inflammatory condition that facilitates tumor development. The cross-talk between inflammation and cancer is linked through extrinsic and intrinsic pathways. While the intrinsic pathway is regulated by genetic factors that cause neoplasia, at the same time the extrinsic pathway is driven by the inflammatory conditions that pose a risk factor to cancer.

Intrinsic pathway

Several studies have exhibited the connection between inflammatory trail and oncogenes. Chemokine-directed macrophages and dendritic cell infiltration characterize human papillary thyroid carcinoma (PTC) (Xie et al. 2020). Rearranged Transfection (RET) protein kinase represents a cascade of genetic events in the pathogenesis of PTC. RET activation induced transcription regulates colony stimulating factors (CSF), IL-1β, cyclooxygenase (COX-2) enzymes and chemokines. Higher levels of all these inflammatory molecules were found in the primary tumors of the patients with lymph node metastasis (Russell et al. 2003). Similarly, activation of oncogenes or inactivation of tumor suppressor genes may initiate the inflammatory process. It is well established that epidermal growth factor receptor (EGFR) tyrosine kinase contributes significantly to lung cancer (Lee et al. 2014). Also, EGFR-mutant non-small cell lung cancer is a single oncogene driven disease, and the genetic alterations worsen the overall survival of the patients probably by activating survival signaling pathways (Hong et al. 2018). Further, studies suggest that nuclear factor-κB (NF-κB), Sp1/Sp3 and other transcription factors regulate COX-2, which is overexpressed in glioblastoma (Xu and Shu 2007) Ras proteins, emanating from cell surface receptors, constitutes an important component of signaling pathways involving GDP and GTP. Oncogenic activation of Ras stimulates

switching between GDP and GTP, which fuels up the Ras-mediated GTP hydrolysis. The disturbance in various cellular processes accelerates the expression and production of numerous inflammatory mediators including IL-8, IL-6 and CXCL1, CXCL8, which confer to tumorigenesis (Quail and Joyce 2013).

Extrinsic pathway

Various culprit factors recognized to trigger tumor-extrinsic inflammation include autoimmune conditions, bacterial and viral infection, smoking, tobacco, obesity, exposure to noxious agents, alcohol consumption (Sherman and Beatty 2023) and others. All these are reported to cause an immunosuppressive TME, which increases the risk of cancer and confers the progression of malignant conditions. Once the inflammatory TME sets in, inflammatory factors from tumor cells, initiates activation of oncogene, and inactivation of tumor suppressor genes. It results in increased proliferation and prolonged cell survival. Colorectal cancer presents a good paradigm of association between inflammatory bowel disease (IBD), a highly chronic inflammatory condition, and cancer. IBD drives through a repeated cycle of wounding and repair (Choi et al. 2017). Modulating this occult evolutionary process are the mediators that orchestrate an inflammatory microenvironment. These mediators comprise of leukocyte infiltration, cytokines and chemokines along with the ROS-induced epigenetic alterations of tumor-related genes including Bcl-2, p53, p16 and adenomatous polyposis coli (Danese and Mantovani 2010).

The treatment targeting the intrinsic pathway of inflammation is one of the breakthroughs in cancer therapy. Several drugs with anti-tumor activity act by blocking the inhibitory signals and act as immune checkpoint inhibitors. Patients responding to T cell inhibitory checkpoint proteins CTLA-4 and PD(L)1 via anti CTLA-4 and anti PD(L)1 therapy demonstrate anti-tumor immunity especially in melanoma and NSCLC patients (Hugo et al. 2016; Rizvi et al. 2015). The response is higher in melanoma and NSCLC patients at checkpoint inhibitor due to high antigenicity via mutational burden compared to adenocarcinoma and colorectal cancer with low antigenicity and mutational burden (Yarchoan et al. 2017). Tumors with high infiltration of T cells or PD1-high T cells with elevated IFNγ gene signature exhibits improve response to checkpoint options (Herbst and Soria 2014; Herbst et al. 2014; Thommen et al. 2018).

FDA-approved checkpoint inhibitors at various stages of clinical trials are currently at different stages of output (Vaddepally et al. 2020). In spite of initial success in lymphoma and melanoma, the results on breast and prostate cancer is not very impressive, the major barrier responsible for limited response in breast and prostate tumor is immune-suppression

in TME (Petty and Yang 2017), with tumor-associated macrophage playing dominant role or providing resistance to immunotherapy at TME(Poole et al. 2021). Further TAM also promotes carcinogenesis via secreting cytokines, growth factors that facilitate migration, invasion and metastasis (Chen et al. 2019). Hence, targeting these TAM-specific checkpoint through NPs may enhance the antitumor therapy.

Augmentation of molecular pathways in cancer development

Several pathways have been deciphered that can lead to development of cancer. However, there are three major pathways well established for multiple malignant diseases. Chromosomal unpredictability leading to instability characterized by altered rearrangement, structural aberration and loss of tumor suppressor gene loci is responsible for major causes of cancer. Unstable chromosomes lead to mutation in KRAS and BRAF pathways which further alters tumor suppressor gene activity including Adenomatous polyposis coli (APC), PIK3KA and SMAD4 (Clapper et al. 2020). Dysfunction of mismatch repair (MMR) genes is often termed as microsatellite instability (MSI) second important pathway associated with mutations followed by third pathway often known as CpG island methylation pathway (CIMP) involving multiple stages of cancer development (Zheng et al. 2021; Lorenzi et al. 2020). KRAS mutation is associated with CIMP low tumors and BRAF along with MLH1 mutation is associated with CIMP high tumors (Ogino et al. 2006). These three pathways are not mutually separated, hence need to be read with each other defining the molecular characteristic pathway of cancer development. Activation of Mitogen-Activated Protein Kinase (MAPK) pathway is associated with serrated pathway along with CIMP mutations (Nakanishi et al. 2019). The mutational alteration in association with recruited immune cells, vascular cells and fibroblast compose TME can well define the cancer evolution (Laconi et al. 2020). Recent important component of TME is linked to the contribution of nerves in pathogenesis of cancer; new evidence suggests that cancer may reactivate nerve dependent developmental and regenerative processes in cancer growth and survival (Zahalka and Frenette 2020). The interaction of these cells closely governs the proliferation, progression, apoptosis, evasion to growth suppression and immune cells, angiogenesis and metastasis along with energy metabolism in alteration of normal cell to cancer cell.

Most of the research pattern is associated with alteration of normal cell to malignant cell, but diversified role of non-cancer cells is equally important in development of full-fledged neoplastic stage. It is observed that TME plays a significant relevant role in the development of cancer, launching consensus molecular subtype (CMS) from CMS

1–4 classification (Binnewies et al. 2018). Hypermutated MSI tumors are characterized by immune cell infiltration, with favorable response to checkpoint therapies and high immunogenic response is representation of CMS1 (Picard et al. 2020). CMS4 are characterized by altered transforming growth factor -β (TGF-β) signals and excess of mesenchymal stroma cells (Luo et al. 2021). Altered TGF-β signaling initiates fibroblast activation that leads to invasion of cancer cells to local tissues, metastasis, angiogenesis and dodged the body defense cells (Bremnes et al. 2011; Chiavarina et al. 2021). It is observed inhibition of TGF-β signaling in fibroblast activates T cell infiltration, with positive output on checkpoint blockade in cells with chromosomal aberration (Gough et al. 2021; Baker et al. 2021). Further, the TME interaction with cancer cells and non-cancer adjacent cell significantly impacts the plasticity and various stages of tumorigenesis, marked by inflammatory response (Tan et al. 2021). Infiltration associated with lymphocytes particularly T helper 1 (Th1) and interferon-γ (IFN-γ) in certain tumors are associated with better prognosis compared to Th17 cell-mediated immune response where prognosis of disease is less favorable (Ren et al. 2021), thus indicating a significant influence of T cells in retarding or accelerating the growth of tumor cells. Immunoscore for cancer is an outcome of cytotoxic and memory lymphocytes presence at the site of disease (Li et al. 2021) in terms of density and position CD8 + and CD3 + cells (Lea et al. 2021) indicating crucial information on invasiveness of disease. Presence of Th2 cells, Th17, regulatory T cells, cells, Natural killer cells (NK), macrophage, b cells and other suppressor governs the variability between the stage and type of tumors (Miller et al. 2022) compare to infiltration of cytotoxic T cells, Th1 cells and memory T cells indicate a better prognosis in all cancers (Nelson et al. 2021). However in spite of all understanding the importance of T cell infiltration in prognosis of patients with microsatellite stability (MSS) and MSI is not sufficient to explain the tumors with MMR deficiency are susceptible to immune checkpoint blockade (Graham et al. 2021). Exploring these checkpoints of inflammation associated with TME can lead to development of novel strategy via nanomedicine in treatment of tumor cells compared to conventional therapeutic drugs.

Cross-talk between inflammatory signaling pathways and nanoparticles

Pathogenesis of cancer is inflammation and time oriented, marked by chronic inflammation that initiates tumorigenesis, tumor induce inflammation and therapy elicited inflammation. All these inflammation stages activate immunosuppressive TME by innate immune cells. Immune and stromal cells synthesize cytokines that regulate inflammatory response,

during inflammation mutated cells are exposed to inflammatory cytokines, acquiring the potential to respond to these signals giving them the lead to grow.

Inflammation leads to cancer

Multiple factors can activate chronic inflammation, such as smoking, inhaled pollutants, dietary DMH falls class of environment factors, infections activating the aberrant immune response, poorly managed inflammatory bowel disease and dietary habits including fried stuff and western diet (Thompson et al. 2015) are the main risk factors cancer associated with activation of inflammation, Fig. 2 details confounding factors that converts a normal cell to cancerous cell based on two factors first that can initiate epigenetic alteration and accumulation of mutants leading to inactivation of tumor suppressor genes or hyperactivation of oncogene, setting a stage for survival and growth (Schmitt and Greten 2021). Second is tumor advancement often termed as promotion, in mutated cells leading to clonal expansion followed by tumor growth (Asada and Kitamura 2021) from these mutant cells and inflammation significantly is an underlying factor for these alterations. It is not essential to have external carcinogen to initiate tumorigenesis, the same is progressed by DNA damage by inflammation (Gillman et al. 2021), via oxidative stress by cells of innate immunity particularly neutrophils and macrophages, releasing high amount of nitrogen and oxygen reactive species at microenvironment of tissue (Teli et al. 2021). These reactive species can break single and or double strand DNA and modify the nucleotide (Zabransky et al. 2022). It is observed inflammation in intestine alters functions of epithelial cells, making intestinal stem cell exposed to environmental mutagens, initiating a cross talk between active inflammatory cells and intestinal epithelial cells (Ramadan et al. 2022), with further intervention by gastric pathogen and commensal having pro-cancerous characteristics (Behrouzi et al. 2022). Chronic inflammation initiated at the site leads to excessive tissue regeneration, proliferation and clonal expansion of tumor cells, with dedifferentiation in normal cells that acquire stem cell like properties (Mackenzie 2022). Many signaling pathways involved in tumor initiation and progression via cytokines are under the influence of inflammation. TGF is release during injury is immunosuppressive cytokine regulates uncontrolled progression of inflammation (Lin et al. 2018) in TME it is utilized by cancer cells for progression (Huang et al. 2021) exerting its effect by binding to type 11 receptor (TGFBR11), with serine/threonine kinase domain, mutation in TGFBR11 gene is often observed in cancer with microsatellite instability, thus inactivating the suppressive effect TGF (Yu and Feng 2019). Further TGF activates epithelial–mesenchymal transition (EMT), increases cell
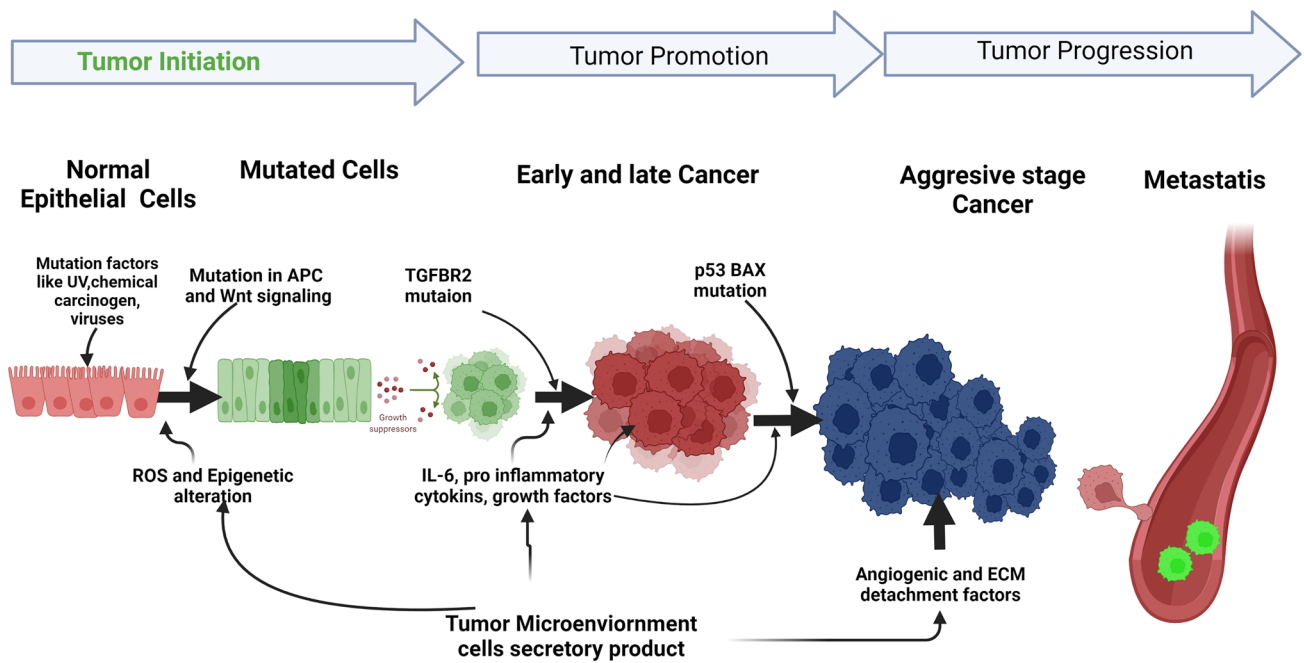
Fig. 2 Figure representing cross talk between various inflammatory mediators: converting a normal cell to cancerous cells through various stages: tumor initiation to promotion further leading to metastasis: activation of ROS, Epigenetics alteration pathways like Wnt. Targeting these intermediated signaling molecules retards the tumor promotion. *(Courtesy biorender.com)*

mobility and ability to invade contributing to tumor invasion, dissemination and development of metastasis observed hepatocellular carcinoma. Similar observations were made in inflammatory breast cancer by EMT via TNF, IL-6 and TGF (Chen et al. 2020). Activation of NF-κB and STAT3 signaling pathway is controlled by inflammatory signaling molecules including TNF, IL-1, IL-6, IL-11 via receptor-mediated intervention (He and Karin 2011) that triggers the transcription of DNA damage response genes to counter the inflammation induce genotoxic effects, making it viable target for nano therapy in treatment of most aggressive cancer disease.

Preclinical studies have demonstrated that the prostaglandins (PGE2) and COX1 potent inflammatory markers have major impact on promotion and growth of cancer, by activating NK-κB signaling, expression of DNA methyltransferases and alteration of TME (Mahapatro et al. 2021; Cui et al. 2021). Inflammation plays a crucial role in invasion and metastasis of cancer cells (Zhang et al. 2021c) via cross talk with epigenetic alteration of cancer associated genes resulting in inhibition of tumor suppressor genes. Expression of DNA methyltransferases DNMT1 and DNMT3 is controlled by TNF, IL-1β and IL-6 (Liu et al. 2021b) thus controlling the NOTCH signaling pathways. Furthermore, Inflammatory response influences other pathways including Wnt and Hippo pathways via micro-RNA's and long non coding RNA's (lnc RNA) important in many cancers' progression via regulating NK-κB and STAT3 signaling in

various cancers. IL-22 produced by neutrophils, Th17 and Th22 and lymphoid cells attempt to express the H19 lnc RNA enhancing the proliferation of colon epithelial cells involved with carcinogenesis (Yadav et al. 2021).

Tumor induce inflammation

Inflammation is key to development of cancer, but many other forms of cancer behave differently under the influence of inflammation. These tumors or cancer induces inflammation via cell-to-cell interaction in a given TME promoting its growth and metastasis (McAllister and Weinberg 2014).

In pathogenesis of several tumors, innate and adaptive immune response along with activation of stromal cells contributes to development of immune response, particularly observed in activation of Wnt in colon cells by (Panneerselvam et al. 2021) product of microbiota in gastric lumen, activating IL-23 expression by myeloid cells, lead to secretion of IL-17 A (Li et al. 2017a), promoting colon cancer (Grivennikov et al. 2012). Furthermore, factors like metabolite products including from the microorganism, break the barrier necessary for signal controlling mechanism initiate the tumor elicit inflammation leading to loss of p53 with activation of NK-κB and STAT3 pathways (Dmitrieva-Posocco et al. 2019), consequently promoting proliferation and survival through loss of tumor suppressor gene and activation of oncogene with indurated tumor elicited inflammation, by

production of proinflammatory cytokines, growth factors and chemokines at the site of tumor (Davidson et al. 2021).

Supply of sufficient nutrients and blood to tumor cells is a key to their survival and growth, insufficient blood supply leads to hypoxia responsible for cell death via necrosis (Emami Nejad et al. 2021), thus producing certain proinflammatory chemicals including IL-1, uric acid or ATP. Hypoxia in tumors, increases expression of hypoxia-inducible factor 1α (HIF1α) along with cells associated with TME with release of TGFβ and CXCL13 from cancer associated fibroblast, initiating the recruitment of myeloid and lymphoid cells at the TME including B cell, monocytes and macrophage in tumors of prostate gland (Yashiro et al. 2021; Ammirante et al. 2014). The local cytokine environment in TME activates inflammatory response for tumor growth and also governs the immunosuppressive activity of immune cells. Cytokines derived from tumors including TGFβ slow proliferation of T cells, suppress the APC nature of dendritic cells, inhibit the function of NK cells, and support the formation of Treg cells (Tauriello et al. 2022). The concentration of TGFβ in TME administers nature and activities of various T cells that controls the establishment of metastasis (Chang and Pauklin 2021) with development of angiogenesis in newly established tumors (Chiavarina et al. 2021). Suppression of TGFβ secretion, can reduce the aggressiveness of tumors (Pawlak and Blobe 2022) reducing the burden and load of inflammation. The same approach is detected by SIRT1/PGC-1 pathway activation mitophagy in intestinal epithelial cells to evade T cell recognition involved in antigen processing (Liang et al. 2020). The inflammation derived via TME depends upon the presence of B cells at the site of tumors, presence of B cells depends upon secretion of TGF β and other cytokines like IL-21, IL-10 and IL-33 (McGettigan and Debes 2021) and can change the nature of IgGs from IgM to IgA (Akdis et al. 2016; Cerutti 2008). An increase number of B cells secreting IgA is observed in many cancer patients (Kim et al. 2021b).

Therapy-induced inflammation

Therapy-induced inflammation is one of the most troublesome morbidities after radiochemotherapy (Safarzadeh et al. 2022), with both anti-tumorigenic and protumorogenic, effects depending upon the cancer type (Lau and David 2019). It is often observed during necrosis cell deaths that releases cellular fragments including DNA, calreticulin, HMGB1 along with ATP activating APC (Festjens et al. 2006; Rosenbaum et al. 2021), this further activates T cell response and alters immunosurveillance (Rosenbaum et al. 2021). Some researchers from experimental studies present the different views and state that necrotic cells promote antitumor and tumorigenic activities (Fournié and Poupot

2018) supported by release of IL-33. Further release of cytokines like IL-1α promotes angiogenesis and metastasis (Matsuo et al. 2009) in colon cancer cells ultimately promoting tumorigenesis. Radiation therapy recruitment of Treg cells (Amoozgar et al. 2021) in glioblastoma and chemotherapy immunosuppressive B cells in malignant tissues (Gu et al. 2021) along with release of TNF, Il-17 and IL-6 from cells of TME (Zhang et al. 2018) promoting the survival of residual cancer cells with contribution to therapy resistance (Mackenzie 2022).

Pharmacological action of nanoparticles

Recent advances in pharmacological applications of nanomedicine have targeted the signaling pathways in inflammation associated with cancer. Solid lipid nanoparticles of oligodeoxynucleotides blocks STAT3 pathway in ovarian cancer cells via increase in expression of cleaved caspase 3, Bax, Beclin-1 with reduction in expression of Bcl-2, procaspase 3 and upregulation of E-cadherin expression (Ma et al. 2015). Curcumin loaded liposome with si-RNA complex inhibits cancer cell growth and stimulates apoptosis via targeting STAT3 pathway in skin cancer tissue (Jose et al. 2017). Further inhibition of STAT3 pathway was observed in nanoparticles formulated in liposomes with short hairpin RNA, in ovarian cell lines A2780CP and A2780ss by blocking the cell proliferation and increase in apoptosis (Jiang et al. 2013). Polylactic acid–glycolic acid PD98059 conjugate nanoparticles of PD98059 is a selective inhibitor of MAPK signal that is effective in inhibition of phosphorylation of ERK in breast cancer (Basu et al. 2009). Doxorubicin loaded with iron oxide nanoparticles inhibits the Wnt signaling pathway in chemo resistant breast cancer via alteration in Axin and E-cadherin expression (Miller-Kleinhenz et al. 2018). Chitosan nanoparticles of Piceatannol interferes with MAPK and PI3K/Akt signaling pathway thereby suppress NF-κB activation, that lead to inhibition of proinflammatory cytokines THF-α and IL-8 in hepatocellular carcinoma (Kadry et al. 2018). Drugs like AZD2014 (vistusertib) and its analog AZD8055 formulated as OX26-PEG-Se nanoparticles inhibits small GTPase, Rheb, phosphorylation causing aberrant expression of Adamts-1 via suppression of mTOR and JAK2/STAT3 pathway in breast cancer (Amani et al. 2019; Sun 2021). Inhibition of mTOR pathway in Hepatic cellular carcinoma, initiates mitochondrial membrane damage, ER stress, ROS generation leads to autophagy by functionalized polystyrene nanoparticles of Isoliquiritigenin (Chik et al. 2019). Compounds like N-(4-hydroxyphenyl) 4-hydroxy-2-quinolone-3-carboxamide-PI3Kα formulated in Gold nanorod inhibits PI3Kα/Akt pathway in breast cancer via inhibition of STAT1 and NF-κB (Mahmoud et al. 2020).

Arsenal of treatment opportunities

Despite a number of options available, a plausible outcome to cancer treatment is still a big challenge. The treatments are often hindered by late and poor diagnosis, patient prognosis, type of cancer, lack of drug specificity, low bioavailability, poor tissue penetration, low half-life, physio-chemical properties of the active therapeutic constituent and drug resistance. Currently, chemotherapies, surgery and radio-therapies are the main avenues for the treatment of cancer. Nevertheless, the intrinsic limitations of the conventional therapies have prompted the medical scientists to develop new strategies with more effective and safer treatment, using advanced technologies. In the field of cancer, the advanced, high throughput screening technology finds its major application in the development of nanoparticles or nanomedicines or (NMs) (Min et al. 2021). NMs are the particulates confined within the range of 10^{-9} microns of size, and within this tiny domain, they exhibit unique appealing features of imaging and diagnosis, cell sorting, drug delivery and targeting (Hoskins 2020). Further applications attributed to nanotechnology include development of vaccines and miniature medical devices, bio-tagging or labelling, bio detection of pathogenic microbes, proteins, DNA probing and pharmacokinetic studies (Salata 2004).

Over the last several decades, nanotechnology has been significantly contributing to oncology in diagnosis, imaging and management of cancer. Nanoparticles (NPs) designed as liposomes, polymeric micelles and albumin NPs have already been approved and currently pursued in the treatment of cancer. Other nano-therapies like chemotherapy, radiotherapy, RNA- and immunotherapy are profusely studied and are under clinical investigations, with promises yet to fulfill in future.

Nanoparticles in inflammation

Cancer nanomedicine is a large platform, over which all physical, chemical and biological sciences are explored by the medical researchers. (NP) are synthesized using one or more materials, and are specifically designed in a manner that they reach directly to the target site on administration. These NPs are used as carriers, and are loaded with anti-inflammatory drugs. These specifically engineered formulations target the inflammatory sensors (macrophages) through phagocytosis, and thus, regulate the expression of pro- and anti-inflammatory molecules. This advanced technology has addressed the major issues of drug bioavailability and toxicity. Moreover, delivery to the target tissues has resulted in low dose and better efficacy of the

therapeutic agent. Further, intracellular delivery of highly specific biomolecular drugs, e.g., DNA, mRNA, siRNA is a great advantage of nanomaterials. Table 1 exhibits some of the innovative and novel approaches of the nanomedicine system, studied pre-clinically on the animal models, for their action on inflammatory disorders.

First clinically approved NPs in the field of cancer therapy were liposomes, and till date various drugs-encapsulated liposomes attract the medical interest. A liposome encapsulating daunorubicin and cytarabine (VYXEOS), in a ratio of 5:1, is used worldwide for acute myeloid leukemia in adults (Blair 2018). Paclitaxel loaded Liposome, demonstrated advantage compared to non NPs in tumor drug accumulation, penetration via suppression of tumor inflammation and immunosuppressive TME (Widjaya et al. 2022). The liposome got FDA approval when it exhibited clinical efficacy in elderly diagnosed with AML in phase-3 clinical trial (Table 2). Similarly, liposomal combinational delivery of Irinotecan and Floxuridine (1:1) is under phase-II clinical trial in patients with advanced colorectal carcinoma (Table 2). Beyond acting as a carrier for chemotherapeutic drugs, NPs can also be hired for the target delivery of other anti-tumor biological drugs including antisense oligonucleotides, small interfering (si)-RNA, mRNA and DNA inhibitor nucleotides (Gupta et al. 2021) and molecular targeting agents (Ashton et al. 2016). A treatment strategy with gene therapy was designed for advanced pancreatic cancer disease, where the liposomes were loaded with siRNA against Protein kinase N3 (Atu07), for its successful delivery at the target site (Table 2). The review is currently under a second phase of the clinical trial (Mainini and Eccles 2020) NCT01808638. In another phase-2 clinical trial, the effects of siRNA against PLK1 encapsulated lipid NPs are being studied on advanced hepatocellular carcinoma. A similar study on solid tumors is under phase-1 trial, where lipid NPs are loaded with siRNA against VEGFA (Hattab et al. 2021) NCT00882180. Similarly, studies focused on breast cancer induced bone metastasis demonstrated siRNA loaded E-selectin thioaptamer multistage vesicles targeting the STAT3 pathway increased the survival time in mice model (MAROTTA et al. 2011). In the breast and lung cancer model RNA interference was able to suppress RAS/MEK/ERK and PI3K/AKT/mTOR pathways countering the cancer metastasis (Saini et al. 2013).

Nano-techniques have enabled the scientists to exploit the naturally occurring biomolecules, and convert them into ideal nanocarriers for DNA, proteins and drugs (Freitag and Wagner 2021). These carriers are formed by the assembly of multiple copies of viral capsid proteins, and are also amenable to site-selective functions, when facilitated by genetic and chemical engineering techniques (Demirer et al. 2021). These viral nanoparticles can be expressed in host cells, purified conveniently and produced in a cost-friendly and eco-friendly manner (Lauster et al. 2020). Adeno-virus

Table 1 Innovative and novel approaches of nanomedicine system, studied pre-clinically on the animal models, for their action on inflammatory disorders

Nanocarrier (Organic/Inorganic)	Active ligand	Dose and route of administration	Nature of disease	Outcomes	References
PEGylated liposomes (Organic)	Prednisolone	10 mg/kg of NPs iv in rats	Renal disease	Accumulated particularly in inflamed kidneys; Increased recruitment of inflammatory macrophages; Decreased production of MCP-1 mRNA	(Van Alem et al. 2018)
Hyaluronic acid coated solid-lipid NPs (Organic)	Prednisolone	15 mg/kg of drug, intra-articular in mice	Rheumatoid arthritis	Selectively Accumulated in the inflamed tissues; Reduction in inflammatory cytokines	(Zhou et al. 2018)
Positively charged PEP–PEG–PBG Polymer micelles (Organic)	Tacrolimus (FK506)	30 μg of formulation topically in C57BL/6 mice	Ophthalmic complications	Significant reduction in corneal epithelium apoptosis; Suppression of TNF-α, MMP9, IL-6 and other inflammatory mediators	(Lin et al. 2019)
Squalene adenosine NPs (Organic)	Tocopherol	15 mg/kg each of NPs and tocopherol, iv in C57BL/6 (male) and BALB/c (female) mice	Reproductive malfunction	Significant decrease in TNF-α and increased production of IL-10; Significant decrease in MCP-1 and IL-6 in lungs and kidney; Improved survival rate in lethal LPS model	(Brusini et al. 2020)
Silicon-dioxide NPs (Inorganic)	Mesalazine	100 mg/kg/day of NPs, oral in BALB/c male mice	Ulcerative colitis	Significant decrease in cytokines TNF-α and IL-6 production	(Tang et al. 2017)
PEGylated liposomes (Organic)	Cyclosporin-A	2.5 mg/kg equivalent of Cyclosporin-A, i.v., in male Westar rats	Neuroinflammation	Significant recovery of infarct size, brain edema and neurological actions as compared to free drug; Reduced TNF-α levels	(Partoazar et al. 2017)
PEGylated liposomes (Organic)	FK506	i.v. injection in male Lewis rats	Autoimmune myocarditis	Increased FK506 concentration in both plasma and heart; Reduced expression of cytokines—interferon (IFN)-γ and TNF-α; Reduced myocardial fibrosis and inflammation	(Okuda et al. 2016)
PLGA NPs (Organic)	Budesonide	42 μg of NPs, p.o., BALB/c mice	Inflamed intestinal mucosa	Selective targeting at the site of inflammation	(Ali et al. 2016)
Dual polymeric NPs composed of Eudragit FS30-D and Eudragit RS100 (Organic)	Budesonide	0.5 mg/kg of drug, p.o., in mice	Colitis	Improved colon-specific drug targeting	(Naeem et al. 2015)

Table 1 (continued)

Nanocarrier (Organic/Inorganic)	Active ligand	Dose and route of administration	Nature of disease	Outcomes	References
Solid lipid NPs (Organic)	Dexamethasone and butyrate	0.1 mg/kg of Dexamethasone and 4 mg/kg of butyrate, p.o., in BALB/c mice	Inflammatory bowel disease	Significant decrease in pro-inflammatory cytokines at the dose 10 times lower than of the free drug	(Dianzani et al. 2017)
PEG-Polycaprolactone polymer micelles (Organic)	Dexamethasone	0.8 mg/kg of Dexamethasone, i.v. in Wistar rat	Rheumatoid arthritis	Suppression of paw swelling and erythema	(Wang et al. 2016)
Nano-sized elastic niosomes (Organic)	Prednisolone	500 µg of prednisolone, intra-ocular in albino rabbits	Ophthalmic complications	Complete healing time reduced to half. Significant reduction in IOP	(Gaafar et al. 2014)
Biodegradable polymeric NPs composed of PLGA-PEG-ColIV (Organic)	Recombinant mouse IL-10	100–500 ng/mouse of equivalent Recombinant IL-10 i.v., in C57BL/6 (female) mice	Advanced atherosclerosis	Reduced levels of IL–6 and TNF-α. Reduced levels of alanine amino transferase	(Kamaly et al. 2016)
NGPEGSS NPs incorporating BAC and PEG polymers (Organic)	Anti-inflammatory cell penetrating peptide KAFAK	50 µg of NPs, on cartilage explants in osteoarthritis model	Cartilage inflammation	Specific targeting of inflamed tissues. Reduced levels of pro-inflammatory cytokines	(Lin et al. 2016)
Chitosan polyglutamic NPs (Organic)	Diclofenac	0.7 mg/ml in vitro human macrophages	–	Rapid internalization without causing toxicity below 0.7 mg/ml in vitro. Increased production of PGE-2. Reduced level of IL-6	(Gonçalves et al. 2015)
Mannose-modified trimethyl chitosan–cysteine NPs (Organic)	TNF-α siRNA	20–50 µg of equivalent of TNF-α siRNA/kg, p.o., in male Sprague Dawley rats	–	Significant TNF-α knockdown at low doses	(He et al. 2015)
Omega-3 FA rich flaxseed oil-based nanoemulsion system (Organic)	Cyclosporine A	5 mg/kg of NPs, intra-nasal, in Sprague–Dawley rats	Neurological disorder	Higher uptake in brain. Inhibition of pro-inflammatory cytokines	(Yadav et al. 2019)
Modified chitosan nanocarrier carrying folic acid, diethyl amine and PEG groups (Organic)	TNF-α siRNA	50 µg of siRNA/kg, p.o., in male Sprague–Dawley rats, 4 inj. i.p., in female DBA/1 mice	Rheumatoid arthritis	Significant decrease in inflammation	(Shi et al. 2018)

Table 2 Nano formulation/Nanomedicine's drug molecules in Clinical trial

Therapy type	Platform	Active ligand	Cancer type	References
Chemotherapy; combinational delivery	Liposomes	Floxuridine + Irinotecan	Advanced colorectal cancer	(Batist et al. 2009) NCT00361842
Chemotherapy; combinational delivery	Liposomes	Cytarabine + Daunorubicin (VYEXOS)	High risk acute myeloid leukemia (AML)	(Kansal et al. 2017) NCT01696084
Chemotherapy, targeted delivery	EGFR-targeting liposomes	Doxorubicin (C225-ILS-DOX)	Solid Tumors	(Mamot et al. 2012) NCT01702129
Chemotherapy, targeted delivery	TfR targeting liposomes	Oxaliplatin	Gastro-esophageal cancer	(Senzer et al. 2009) NCT00964080
Chemotherapy, targeted delivery	HER-2 targeting liposomes	Doxorubicin	HER2 positive breast cancer	(Miller et al. 2016) NCT02213744
Nab-rapamycin	Rapamycin	Malignant advanced PE-carcinoma or advanced cancer with mTOR mutation		(Wagner et al. 2020) NCT02494570 (Gonzalez-Angulo et al. 2013) NCT02646319
Chemotherapy, non-targeted delivery	Liposomes	Paclitaxel	Pancreatic carcinoma, liver cancer, HER-2 negative and TNBC	(Su et al. 2019) NCT00377936; (Fasol et al. 2012) NCT00542048; (Ignatiadis et al. 2016) NCT01537536; (Ignatiadis et al. 2016) NCT00448305
Radiotherapy	Hafnium oxide NP	–	Soft tissue sarcoma	(Brivio et al. 2017) NCT02379845
Gene (RNAi) therapy	TfR-targeting liposomes	Plasmid encoding human p53 DNA	Recurrent glioblastoma; metastatic pancreatic cancer	(Phase 2017) NCT02340156; (Kundranda and Dragovich 2016) NCT02340117
Gene (RNAi) therapy	Liposomes	DNA oligonucleotide against BCL-2	Relapsed non-Hodgkin lymphoma, diffused large B-cell lymphoma	(Harb et al. 2014) NCT01733238
Gene (RNAi) therapy	Liposomes	siRNA against protein kinase N3	Advanced pancreatic cancer	(Nikam and Gore 2018) NCT01808638
Gene (RNAi) therapy	Lipid NPs	siRNA against PLK1	Advanced hepatocellular carcinoma	(Strumberg et al. 2007) NCT02191878
Gene (RNAi) therapy	Lipid NPs	siRNA against VEGFA	Solid tumors	(Multi-center 2012) NCT01158079
Immunotherapy	Liposomes	Recombinant HER2 antigen	Metastatic breast cancer	(Curigliano et al. 2016) NCT00952692
Immunotherapy	Lipid NPs	Plasmid DNA	Relapsed leukemia	(Tyagi and Santos 2018) NCT00860522
Immunotherapy	Colloidal gold NP	TNF	Advanced solid tumors	(Corti et al. 2021) NCT00356980

approved as a gene therapy for lipoprotein lipase deficiency (Ylä-Herttuala 2012), lentivirus as a gene therapy for cancer and other diseases, and tobacco-mosaic virus for cancer therapy in experimental animals (Czapar et al. 2016) include few examples of viral NPs.

Further, exosomes, the extracellular vesicles of 40–160 nm, secreted by many eukaryotic cells, consist of DNA, mRNA, circular RNA, microRNA, messenger RNA have been used as a novel mode of prognostic markers for grading of tumors (Table 2). The intercellular communication between exosomes and TME creates a platform for tumorigenesis, invasion, metastasis and drug resistance. On this ground, cancer-related exosomes have been technologically engineered to carry tumor-suppressing proteins, nucleic acid components, or targeted drug functions, and act as precision medicine (Dai et al. 2020; Yang et al. 2021).

Not only biological, but novel inorganic NPs like nano-diamond (Wang et al. 2021d) and graphene (Mariadoss et al. 2020) have also attracted a significant attention of the

researchers in cancer therapy. Innovation in nanotechnologies is a continuous process. Table 2 elicits some of the examples of nanomedicines, which are either approved by FDA, or are under clinical trial, for their use as a therapy for cancer. NPs can be structured to deliver multiple active pharmaceutical agents at a time, thereby facilitating a synergistic approach to cancer therapy avoiding and the drug resistance. Immunotherapy, which customizes the immune system to target the cancer cells, has moved out from laboratories to the clinical applications, and has shown successful outcomes in hematological and solid cancers (Goldberg 2019). Excellence of immunotherapy, however, is hindered by some major factors including lack of effective options for some cancer types, patients' unresponsiveness, emerging therapy resistance, immunosuppressive TME and life threatening immune-toxicities (Radwan et al. 2019). Advancement in nanotechnology for delivery of drug and ideal clinical outcomes of immunotherapy, if converged together on the same platform, there would be a high potential of obtaining an ultimate momentum in cancer treatment (Bockamp et al. 2020) NPs have been increasingly recognized as adjuvant carrier for vaccines, with increased tissue permeability, sustained release of antigens and favorable uptake by APCs (Editorial 2020). Biologic drugs like monoclonal antibodies, when administered for cancer immunotherapy, may result in the formation of anti-drug antibodies, hampering their efficacy and potency. Newly engineered tolerogenic NPs appear to address these issues (Thorp et al. 2020; Kishimoto 2020).

EPR—the platform for NP delivery

Passive targeting

Enhanced permeability and Retention (EPR) effect, first introduced in 1986 by Matsumura and Maeda, has been increasingly studied over time. Pathophysiological characteristics of EPR vary substantially with tumorous and healthy tissues of a patient. It has been realized that the EPR effect is heterogeneous and changes with the progression of tumor (Golombek et al. 2018; Sindhwani et al. 2020). It has been recognized as an important platform for NP delivery to solid tumors. Low MW drugs are easily extravagant out of the blood vessels and accumulate in the healthy tissues, while, on the other hand, abnormal wide fenestrations in tumor results in retention of nanodrugs, up to several hundred nanometers in size, at the pathological sites. This, along with lack of lymphatic drainage, limits the accumulation of NPs in tumors (Fig. 3). As a consequence, clinical outcomes of nanoparticles fluctuate (Rosenblum et al. 2018; Sindhwani et al. 2020). To translate the NPs from clinical research successfully to clinical application, and facilitate personalized cancer therapy, it is important that efficient passive targeting NPs should be designed, which can selectively target the tumor cells through EPR (Yao et al. 2020; Zhao et al. 2016). A combined effect of pharmacological and
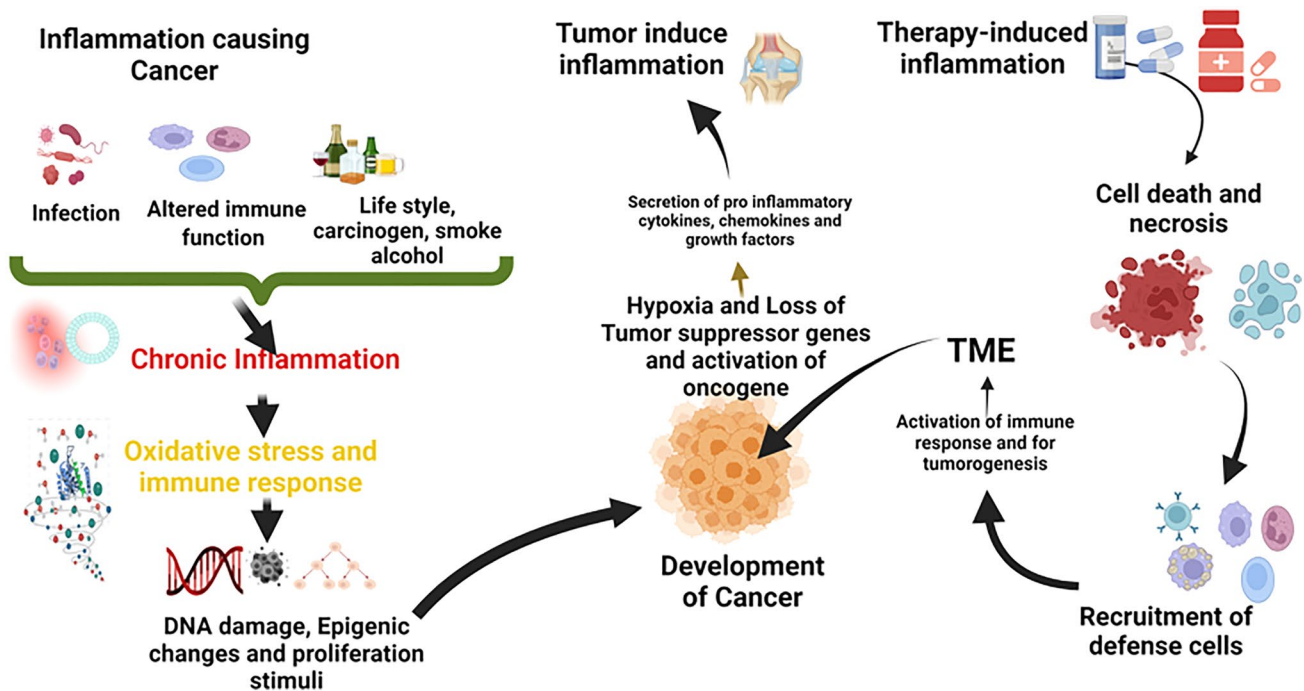
Fig. 3 Mechanisms overlapping and cross talk between tumor and therapy induce inflammation with inflammation-induced tumor *(Courtesy biorender.com)*

physical (hyperthermia and radiotherapy) approaches can be employed to enhance the accumulation of EPR-based nanocarriers in the tumor tissue, and thus increase the treatment efficacy. Researchers have attempted to combine the drug carriers with functionalized physical, biological or chemical ligands to improve passive and active targeting strategies (Nguyen et al. 2021). Daunoxome, Marqibo, Onivyde, Genexol-PM, CPX-1, AZD2811 and EndoTAG-1 are few examples of passively targeted NPs currently used clinically with a better pharmacokinetic profile (Wilhelm et al. 2016). Currently, a liposome encapsulated Doxorubicin (C225-ILS-DOX) was formulated (Table 2), where delivery efficacy was further increased by attaching antibody fragments to its surface. This immuno-liposome selectively delivers Doxorubicin to the overexpressed EGFR, and is currently under phase-1 trial (NCT00361842). for its effect on solid tumors (Batist et al. 2009) Similarly, MBP-426 is an Oxaliplatin-encapsulated liposome (NCT00964080) that targets overexpressed Transferrin, and is indicated for gastroesophageal carcinoma (Senzer et al. 2009). The drug passed phase-1 trial, and is currently under phase-2 clinical trial (Table 2). MM302, a doxorubicin-loaded liposome, modified with HER-2 targeting antibodies was tested for its efficacy in advanced HER-2 positive breast cancer; (Table 2). However, the insignificant benefits led to the discontinuation of trial in 2016 (Miller et al. 2016) (NCT02213744). CPX-351, a liposome holding the composition of cytarabine and daunorubicin, improved overall survival of the patients with high-risk acute myeloid leukemia (Lancet et al. 2016). Most prominent pharmacotherapies are the drugs modulating VEGF signaling, TNF-α, angiotensin agonists and blockers and nitric oxide producing drugs (Zhang et al. 2021a).

EPR heterogeneity within and between different tumors may impact the clinical outcome of passively targeted carriers. Non-uniformity in the endothelial gaps may result in imbalanced extravasation of NPs into the tumor. Studies suggest that NPs penetration in the tumor periphery is more frequent than that in the core (Park et al. 2019). Not only permeability, but factors like perfusion and physio-chemical properties (including particle size, shape and elasticity) of NPs also govern their extravasation and deposition (Xu and Kleinstreuer 2019). An in vitro comparison of three different sizes, 20, 50 and 200 nm, of silica conjugates exhibited that the 50 nm particle had highest penetration and retention in the tumor cell and had maximum efficacy (Jin et al. 2018). Xie et al. designed and evaluated the effects of varied shapes of MPE-glycol coated gold nanoparticles, where triangles-shaped carriers exhibited maximum efficiency, followed by rods and stars (Xie et al. 2017). Further, polymer elasticity of nanocarriers may also impact the efficient tumor delivery. Guo et al. studied the tumor uptake efficiency of nanolipogels, and observed that neoplastic and non-plastic carriers presented significantly higher uptake as compared to elastic carriers. It was further reported that neoplastic nano-carriers accumulated and retained in the tumor cells, while the elastic ones deposited in liver (Guo et al. 2018). Similar findings correlating elasticity of nanocarriers to their biological effects have also been reported by Bashyal et al. where softer nanoparticles significantly accumulated and prolonged the systemic circulation in vivo, as compared to the elastic carriers (Bashyal et al. 2021). Though, the nano-carriers tend to increase the drug delivery at the target site as compared to the free chemotherapeutic drugs, however, the meta-analysis of preclinical data of over a decade suggests that only about 0.7% of the injected dose of nanocarriers reaches the target site (Ouyang et al. 2020).
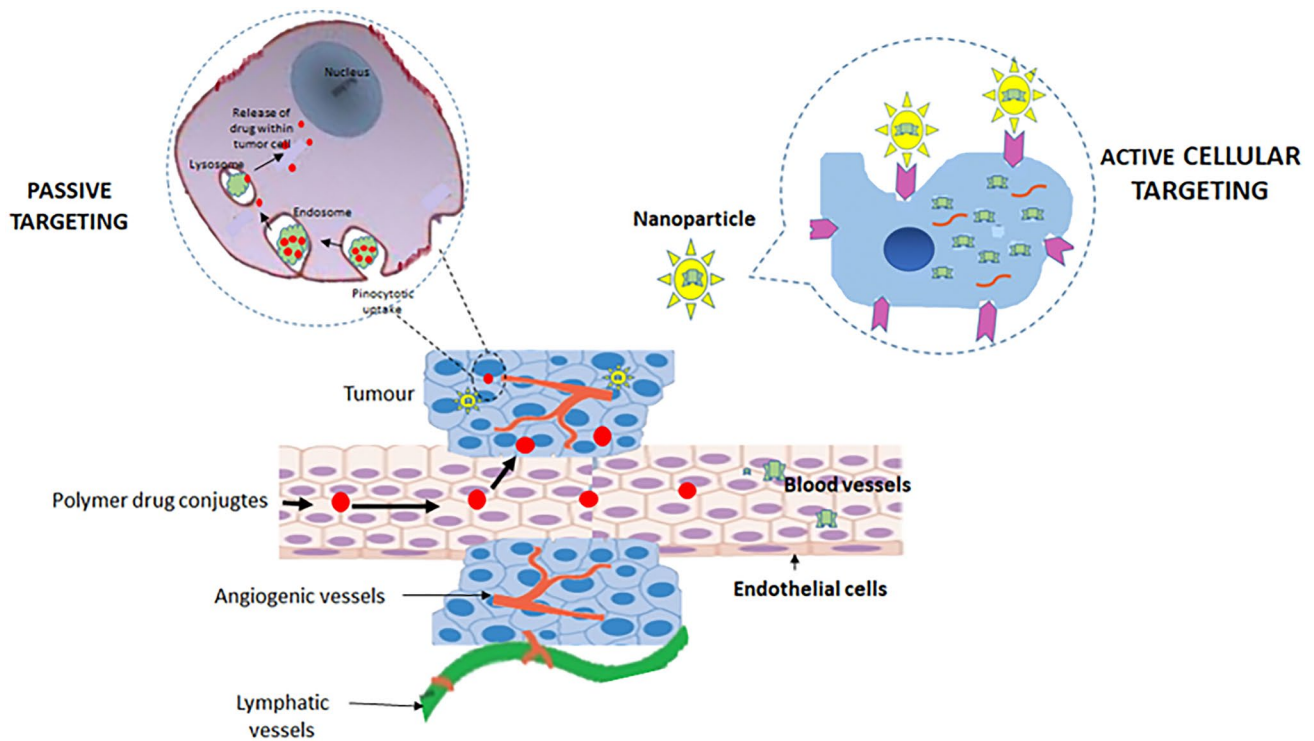
Active targeting

By increasing the target efficiency and retention of nanoparticles, the researchers developed the concept of active cellular targeting, as a complementary technique to passively targeting carriers. This technique, which enhances the delivery of high molecular weight and rapidly enzymatic degradable molecules, involves the incorporation of targeting ligands on the surface of nanoparticles (Wang et al. 2021c; Zhang and Kohane 2020) (Fig. 4). These ligands have affinity to bind with the receptors, like $\alpha v\beta_3$, $\alpha v\beta_5$ and $\alpha_5\beta_1$ integrins, overexpressed on the tumor endothelial cell surface (Slack et al. 2021; Nestić et al. 2021). Preclinical in vitro studies have revealed that inhibition of angiogenesis may result in suppression of existing tumors and metastasis regression (van Alem et al. 2021). Kim et al. showed that silencing of endothelial genes like VEGFR1 or delta-like protein 4 (DLL4), which are involved in angiogenesis, low molecular weight NPs efficiently delivered si-RNAs to endothelial cells, and reduced the growth and metastasis of mouse Lewis lung carcinoma (Kim et al. 2021a; Dahlman et al. 2014). However, the endocytic pathway poses one of the major barriers and may cause a detrimental effect on the fate of the nanocarriers. NPs channelized through ligand-mediated endocytosis may eventually be degraded in the lysosomes (Dutta et al. 2021). These challenges have restrained the actively targeted NPs to be used clinically till date; however, significant efforts in development and modifications in engineering these techniques are continuous in the pipeline.

Bridging drug delivery to the tumor

NP–protein interactions

When a NP is exposed to a biological system, several biomolecules, especially proteins, rapidly cover its surface, resulting in formation of a corona (Park 2020). This gives

Fig. 4 Passive and active targeting via nanoparticles

NPs a biological identity and changes its physiological response in terms of cellular uptake, intracellular trafficking, cellular distribution, retention and clearance. and pharmacokinetic properties. Opsonization, for instance, triggers clearance by mononuclear phagocytosis, while apolipoproteins and albumin, on the other hand, facilitate stealth effects of NPs and improve their delivery to specific organs. Many studies are being conducted in vitro with an attempt to direct the NP-corona composition to increase the drug delivery to tumor cells(Khan et al. 2022), Though, further advancement in this field is still to be addressed.

Blood circulation

In addition to the mononuclear phagocyte (MP) uptake system, systemic circulation can also govern the efficiency of NPs. Longer circulation time ensures longer contact of NPs with the target tissue, which in turn, be affected by renal excretion. The glomerular barrier restricts the filtration of macromolecular proteins, while rapidly filters water and small molecules. Likewise, the global filtration of NPs circulating in the blood relies on their size, surface charge and hydrophilicity (Ruan et al. 2021). It is established that the NPs > 6 nm can efficiently cross the glomerular barrier (Mosleh-Shirazi et al. 2021). Further, with richly profuse tissues and particles with efficient extravasation from

microcirculation, the NPs even with short systemic half-life may suitably accumulate in the tumor. Conversely, less perfused tissues or particles with low extravasation require a longer circulation half-life to enhance their acquaintance in the TME, thereby progressively increasing extravasation. Several advances in designing and fabricating of polymeric NPs have been made rendering them long serum-circulating characters. The most recent method to camouflage the NPs is to graft or conjugate their surfaces with polyethylene glycol or polysaccharides and other hydrophilic polymers (Subhan and Torchilin 2021; Hu et al. 2018). In a randomized phase-3 study, PEGYlated liposomal cisplatin, combined with paclitaxel were studied on non-small-cell lung cancer (Table 2). It resulted in significantly low toxicity as compared to the original cisplatin and paclitaxel combination (Nan 2019). Other similar studies were conducted targeting ovarian and HIV-related Kaposi sarcomas by doxorubicin encapsulated PEGYlated liposomes (Table 2). However, the non-specific interaction between PEG-NPs and serum proteins (as discussed above) limit the circulation time, and promote opsonization and MP action (Abbina et al. 2020). Also, multiple administration can result in development of circulating anti-PEG antibodies, which may develop severe hypersensitivity reactions. Wang et al. studied the clearance rate of various PEGylated molecules like PLGA-NPs and liposomes on lung cancer, and observed that even a single administration of PEG-PLGA-NPs triggered the production

of anti-PEG immunoglobulin (Ig) M and enhanced the NP's clearance. It not only resulted in reduced circulation time on second administration of PEG-PLA-NP and increased its clearance, but also induced immune reaction towards PEGylated NPs and liposomes (Wang et al. 2021b).

Another strategy to enhance the NP circulation time in blood is a biomimetic approach, where NPs are coated with cell membrane allows the NP surfaces to recapitulate the features of cells, and the membrane proteins render them a biological identity as they appear to be part of the same organism ('Self' recognition) (Liu et al. 2021a). Cell membrane coatings camouflage NPs as biological components, and provide them a longer circulation, avoid opsonization and inhibit the development of NP immunoglobulin antibodies (Papini et al. 2020). The chemical conjugation of NPs surfaces with cell markers prevents the normal cells from activating the MP system. At the same time, decorating NPs surfaces with erythrocytes, thrombocytes and leukocytes, help to reduce MP elimination (Brenner et al. 2021). As it appears to be an ideal solution, a wide array of NPs were coated with cellular components like RBCs, platelets, exosomes and leukocytes (Song et al. 2022). RBC-coating provided the increased circulatory half-life to the NPs by passive targeting. However, the ability of platelets to bind to the damaged blood vessels, not only enhanced the circulation time, but also conferred active targeting properties to the nanoparticles (Wang et al. 2020).

This approach was further advanced with the implication of leukocytes as the NP-coating material, relying on their characteristics of circulating cells, possessing still 'Self' proteins, (Liu et al. 2019) tendency to adhere to inflamed vessels, extravasating the surrounding tissues and interaction with foreign bodies. NPs camouflaged with leukocytes, thus can exhibit active targeting not only for tumors, but also for chronic inflammatory conditions.

Recently, a silicon-based biomimetic NPs, co-loaded with IR780 (a near infrared fluorescent dye) (Hu et al. 2021) and doxorubicin (a chemotherapeutic drug) was designed, with its surface camouflaged with a hybrid of leukocytes and platelets (Zhang et al. 2021b). The nanoplatform was studied to target Triple Negative Breast Cancer (TNBC). The hybrid-membrane NPs exhibited an excellent TNBC targeting potential in vivo and in vitro (Liu et al. 2021c). It induced apoptosis and synergistic toxicity in TNBC mice, and suppressed the tumor growth.

Bio-membrane-camouflaged NPs bear dual characteristics—intrinsic features of the cells that served as shielding material, and the functional versatility of the encapsulated nanoparticle (Jin and Bhujwalla 2020) It opens the doors to new opportunities for enhancing the circulation life, reducing immunogenicity and targeting inflammatory and tumor cells. Though these biomimetic technologies appear to possess promising outcomes, there are several miles to cover

before implementing them from clinical applications. The major challenges are the complexity and heterogeneity of the inflammatory/tumor microenvironment, and the cost of designing and synthetic processes. Large-scale production of these biomimetic NPs without batch to batch variation, and scarcity of shielding cells within the body are the other challenges to be faced (Zeng and Pu 2020). Though, 'self'-coated NPs possess a longer circulation half-life, as compared to uncoated ones, however, it is much shorter than that of the cells themselves. Much efforts are thus required post-NPs surface coating, to examine the cellular changes in membrane, its components and elasticity.

Uniform and reproducible synthesis—a gap to loop for clinical translation

Establishing adequate physicochemical characteristics is the most crucial factor in the development of a therapeutic nanoparticle. Appreciable number of factors have been identified that promote tumor extravasation and diffusion, cell targeting and internalization, and steady drug release (Ruan et al. 2021; Ortiz-Casas et al. 2021).

However, the rapid, precise, reproducible and exhaustive production of NPs with distinct features is a big demand, which renders the systematic parallel screening of the large myriad of NPs difficult. This poses a big challenge to maintain uniformity and reproducibility in physical and chemical characteristics of NPs in batch to batch production (Yan et al. 2020). Novel microfluidic technologies are an attempt to answer this challenge, which produce high-speed, self-assembling NPs, with reduced particle size, controllable physical and chemical characteristics, and greater batch-to-batch uniformity (Garcia-Cordero and Maerkl 2020; Monjezi et al. 2021).

Conclusion and future perspectives

Medical science has witnessed great revolutionary advances over the past few decades; however, the nano-medicines for cancer and chronic inflammation are still to mature before their full impact can be recognized and appreciated. Diving into the tumor heterogeneity and identifying EPR markers will open the path to maximal responsiveness to the nanotherapy. Further, a deep understanding of delivery of NPs to the tumor cells, targeting NPs to the tumor microenvironment or the pre-metastatic niche and the NP–bio-interaction will enhance the safety, efficacy and more promising outcome of the nanotherapeutics. A uniform and reproducible synthesis of NPs, their screening and evaluation will drive them to clinical translation. Although many FDA-approved nanocarriers are encapsulated with the chemotherapeutic or anti-inflammatory

drugs, our medical scientists can further progress to incorporate the nanomedicines with novel entities like mRNA, siRNA and kinase inhibitors in near future. Preclinical trials with these entities have shown some plausible outcomes. Further the major cause of cancer deaths attributed to metastatic characteristic, inhibition of signaling cascade by therapeutic intervention of nanoparticles involved in inflammatory mechanism can limit this disease from systemic to localized disease state. The systemic signaling can be blocked by inhibition of circulating inflammatory factors. Recombinant G-CSF has shown promising outcomes on cancer patients with myelosuppressive therapy. Anti-angiogenic, anti-VEGF therapies alters mobilization of cells from bone marrow influencing the cancer development, promoting a strategy to make a new option in treatment of aggressive cancer. Finally, clinical studies will allow oncologists to precisely identify the patients who may be benefited from nano therapy at time when promotion or progression of tumor initiates. Further the cells secreting proinflammatory molecules either neutrophils or lymphocytes need to be monitored on regular interval to stratify the treatment options and nanomedicine can play a decisive role in countering such secretions. More research needs to be carried out both at preclinical and clinical level that can predict low toxicity of chemotherapeutic agents linked with anti-inflammatory potential challenging the inflammation associated signaling pathways, in a wide variety of cancers in discrete populations of neoplasia patients. This article highlights the progressive advances being made in nanotechnology, and reflects the need and importance of further development for the successful clinical translation of nanotherapeutics. We assume that the nanomedicines, in near future, will shift the paradigm of treatment of cancer and chronic inflammatory conditions to the plausible outcome with improved patient survival.

Availability of data and materials The data are available on the request to the corresponding author.

Declarations

Conflict of interest None.

Ethical approval No ethical approval required.

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