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REVIEW ARTICLE

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Role of therapeutic agents on repolarisation of tumour-associated macrophage to halt lung cancer progression

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ABSTRACT

Tumour-associated macrophages (TAMs) represent as much as 50% of the solid mass in different types of human solid tumours including lung, breast, ovarian and pancreatic adenocarcinomas. The tumour microenvironment (TME) plays an important role in the polarisation of macrophages into the M1 phenotype, which is tumour-suppressive, or M2 phenotype, which is tumour promoting. Preclinical and clinical evidences suggest that TAMs are predominantly of the M2 phenotype that supports immune suppression, tumour growth, angiogenesis, metastasis and therapeutic resistance. Hence, significant attention has been focussed on the development of strategies for the modification of TAMs to halt lung cancer progression. The promotion of repolarisation from the M2 to the M1 subtype, or the prevention of M2 polarisation of TAMs in the stromal environment is potential approaches to reduce progression and metastasis of lung cancer. The focus of this article is an introduction to the development and evaluation of therapeutic agents that may halt lung cancer progression *via* the manipulation of macrophage polarisation. This article will address recent advances in the therapeutic efficacy of nanomedicine exploiting surface functionalisation of nanoparticles and will also consider future perspectives.

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Cancer; lung; nanomedicine; therapeutic agent; tumour-associated macrophage

Introduction

Cancer is a global health burden and a leading cause of death. Among the various cancers, lung cancer is the most frequently diagnosed cancer worldwide, accounting for approximately 11.6% of the total cancer mortality [1]. New cases of lung cancer in both sexes are close to 1.8 million, and the number of deaths associated with lung cancer is nearly 1.6 million annually [2]. Signs and symptoms of lung cancer are highly unpredictable because of the heterogeneity of the disease, which can grow in various areas of the respiratory tree [3]. As the result of the lack of proper diagnostic tools to detect lung cancer at an early stage, most lung cancer patients (70%) are diagnosed with advanced disease, which is ultimately reflected in the poor five-year survival rate [2]. Based on histology and immunohistochemistry, lung cancer can be classified into two major groups: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). Nearly 80–85% of lung cancer patients are diagnosed with NSCLC, which includes adenocarcinoma (represents 40% of cases), squamous cell (epidermoid) carcinoma (represents 25–30% of cases), large cell (undifferentiated) carcinoma (represents 10–15% of cases) and other subtypes [4]. While representing only 10–15% of cases, SCLC is the most lethal type of lung cancer with high metastatic potential [4]. Therefore, knowledge of the tumour microenvironment (TME) is important both for earlier diagnosis and for effective treatment in order to improve patient survival. Moreover, tumorigenesis is initiated at the favourable and supportive tumour growing [5]. Although the initial focus on intrinsic factors in cancer cells that correlate with strategies for cancer treatment has been on NF-κB, DNA damage machinery, ABC transporters and apoptotic regulators [6,7], attention has moved towards assessing the role of the TME, which comprises the supporting stroma, including immune cells, extracellular matrix proteins, fibroblasts and vascular endothelial cells [8]. These studies on the TME have revealed the particular importance of immune cells, on tumour growth [8,9]. Depending on the tumour type, the prevalence of immune cells, such as macrophages and mast cells, could lead to an immunosuppressive TME that will promote cancer growth [10]. Macrophages are the most abundant stromal cells within the TME; which instead of providing a tumoricidal action, these cells adopt a pro-tumorigenic role *in vivo* [11]. Subversion of the tumoricidal role of the macrophages results from the presence of immunosuppressive cytokines, growth factors, and hypoxic conditions within the TME, which convert them to tumour-associated macrophages (TAMs) [12]. TAM-induced progression of tumours is preceded by the promotion of angiogenesis, increased motility, tumour invasion, uncontrolled growth, intra- and extravasation and suppression of T-cell responses [13]. Alternatively, prevention of macrophage accumulation within the TME was shown to inhibit tumour progression as well as to prevent metastasis; this opens new platforms for the treatment of cancer through re-educating and re-programming the TME. Several therapeutic agents have been identified against different categories of lung cancer, where control of TAMs is reflected by the effective control of cancer progression. Previous studies have indicated that prevention of TAM infiltration within the TME is implicated in the actions of several drugs which are effective *via* different mechanisms; these include imatinib [14], β-elemene [15], resveratrol (RES) [16], paeoniflorin (PF) [17], hydroxychloroquine (HCQ) [18], astragaloside IV (AS-IV) [19], puerarin [20] and gefitinib [21].

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Strategies in delivery of chemotherapeutics is a great challenge to the formulation scientists. Nowadays, they have adopted unique tools under the umbrella of nanotechnology, to improve the cancer-oriented delivery systems with the objective of safe, selective, preferential and effective delivery. These delivery systems not only improve the pharmacokinetic parameters of the entrapped chemotherapeutics, but also able to overcome the restrictions of biological barriers and even multi-drug resistance [22,23]. Thus, the nanoranged particles (10–1000 nm) of these nanocarriers alter the physiochemical properties of the entrapped drugs, which retain within the systemic circulation for prolonged period by enhanced permeation and retention (EPR) effect to target passively within the highly vascularised TME, whereas surface modification with tumour-specific ligand leads active targeting of the delivery tool [24,25]. Progress in this field has brought several components to the bedside of the patients for treatment and diagnostic purpose of different ailments, and numerous formulations are under clinical investigational stage [26]. Therefore, applications of this multidisciplinary field through nanomaterials and other nanotechnological approaches offer essential breakthrough in the combat against increasing incidences of cancer. This article has focussed on TAM-associated progress of lung cancer, involvement of different therapeutics in the manipulation of macrophage polarisation, and introduction of nanomedicine as an effective tool to overcome the challenges in lung cancer. Therefore, before introduction on different therapeutics and nanotechnological approaches, the relationship between TAMs and uncontrolled growth of cancer cells is discussed in the following section.

Involvement of tumour-associated macrophages in lung cancer progression

Macrophages are polarised into two functionally discrete phenotypes, M1 and M2. Micro-localisation of the macrophages within the tumour islets indicates a noticeable advantage for survival; on the other hand, increased macrophage accumulation within the stromal environment of cancer is associated with poor prognosis in NSCLC [27–29]. Polarisation of the M_1 phenotype is prompted by tumour necrosis factor-α (TNF-α), lipopolysaccharides, interferon-γ and granulocyte-monocyte colony-stimulating factor, whereas the M2 form is promoted by interleukin (IL)21, IL13, IL10, IL4, activin A, glucocorticoids and immune complexes [29]. The M1 phenotype is known to induce the production of IL1, IL6, IL12, IL23, CXC ligand-10, TNF-α, human leukocyte antigen-DR, inducible nitric oxide synthase, and reactive oxygen and nitrogen intermediates [28,29]; on the other hand, the M2 form induces expression of IL10, CD163 antigen, galactose receptor, mannose receptor, arginase-I, scavenger, CC-ligand-22 (CCL-22) and IL-1 receptor antagonist [29,30]. Therefore, M1 macrophages have an anti-tumorigenic action through type-I pro-inflammatory cytokines and participating in antigen presentation; alternatively, M2 macrophages have a pro-tumorigenic role *via* type-II cytokines, promoting inflammatory responses, producing angiogenic factors, cathepsins and metalloproteases, with subsequent suppression of the production of reactive nitrogen intermediates and of antigen presenting properties [31]. In support of this, Ohri et al. stated that the presence of the M1 phenotype in the tumour islets is associated with extended survival of patients with NSCLC [32]. Macrophages are functionally plastic, where M2 converts to M1 when exposed to M_1 cytokines, and *vice versa* [33,34]. For example, conversion of M2 to M1 in Lewis lung carcinoma is related to the presence of TNF-α and downstream of Toll-IL-1 receptor domain-containing adaptor molecule-1/toll-like receptor-3 (TLR-3) [35], whereas the repolarisation of M2 to M1 phenotype by miR155 overexpression in TAMs has been reported [36]. Tumour progression is facilitated by both non-immune and immune mechanisms of TAMs [37].

Non-immune mechanisms provide an important gateway for the development of tumours and their distal seeding; this includes the process of angiogenesis and metastasis [38]. Survival of tumour cells needs angiogenesis, because growing cells require nutrients; moreover, when grown beyond 2–3 mm^3, tumours metastasise through the vascularisations [39]. Experimental evidence demonstrated the influence of TAM-derived epidermal growth factor (EGF) in the migration of tumour cells from the destroyed sections [40,41]. Moreover, the release of EGF is a paracrine response to tumour-derived colony stimulating factor 1 (CSF-1) *via* a positive feedback cycle. Thus, TAMs plays an essential role during the angiogenic switch from benign to malignant tumours through the destruction of the barriers in TME and the production of migratory fuels for metastases of cancer cells [40,42,43]. Further evidence for this role of TAMs is the impairment of tumour angiogenesis following inhibition of TAM-induced pro-angiogenic molecules within the TME, and the ablation of TAMs through the administration of nuclear materials, or by the inhibition of tumour-generated TAM chemo-attractants [44]. Hypoxic conditions within the stromal environment, together with the generated cytokines, facilitate macrophage attraction into the TME; this subsequently induces the production of hypoxia-inducible factor 2α (HIF-2α). Angiogenesis is then promoted *via* the production of vascular endothelial growth factor (VEGF) by the action of HIF-2α [45]. Additionally, TAMs induce the production of other pro-angiogenic cytokines, such as IL-1 (that upregulates HIF-2α), matrix metalloproteinase-9 (MMP-9) (that induces production of VEGF), TNF-α and urokinase-type plasminogen activator (Figure 1) [39]. In breast cancer cells TAM-produced CCL-18 was shown to stimulate both angiogenesis and the tumour development; Wnt7b released from TAMs also induces VEGF production to potentiate angiogenesis [46].

TAM-induced immune mechanisms for the progression of cancer include diminution of antigen presenting abilities, weakening of T-cell activation, stimulation of T-regulatory cell (Treg) functionality and abolition of M1 phenotype-facilitated innate immune responses [37]. As discussed earlier, the predominant tumoricidal role of M1 phenotype of TAMs is due to the production of IL-12 cytokine; however, conversion to the M2 phenotype results in an inability to produce IL-12. Thus, in these cells, the lack of IL-12 precludes the activation of an anti-tumour response mediated by cytotoxic T-lymphocytes (CTLs), natural killer (NK) cells and T-helper type-1 (Th1) cells. Additionally, the M2 phenotype produces IL-10, which in turn induces polarisation of Th2 cells from Th1 cells [37], thereby increasing the production of IL-4 from Th2 cells, this further stimulating the M2 TAM phenotype [47]. Concomitantly, stimulation of CCL22 production from M2 TAMs attracts Tregs, which maintain the suppression of the immune system through an increased level of IL-10. Furthermore, two other immunosuppressive substances, prostaglandin E_2 (PGE_2) and transforming growth factor- β (TGF-β), are also linked to M2 TAMs [39]. Along with the production of TGF- β, M_2 TAMs can transform latent TGF-β to its active state [48]. PGE2 and TGF-β are known to play a potential role *via* altering tumoricidal capacity and T-cell activation [49]. Iriki et al. reported activation of signal transducer and activator of transcription 3 (STAT3) *via* the IL-6 and CCL-4/macrophage inflammatory protein-1β pathway in the stromal environment; this induces tumour cell proliferation and invasion

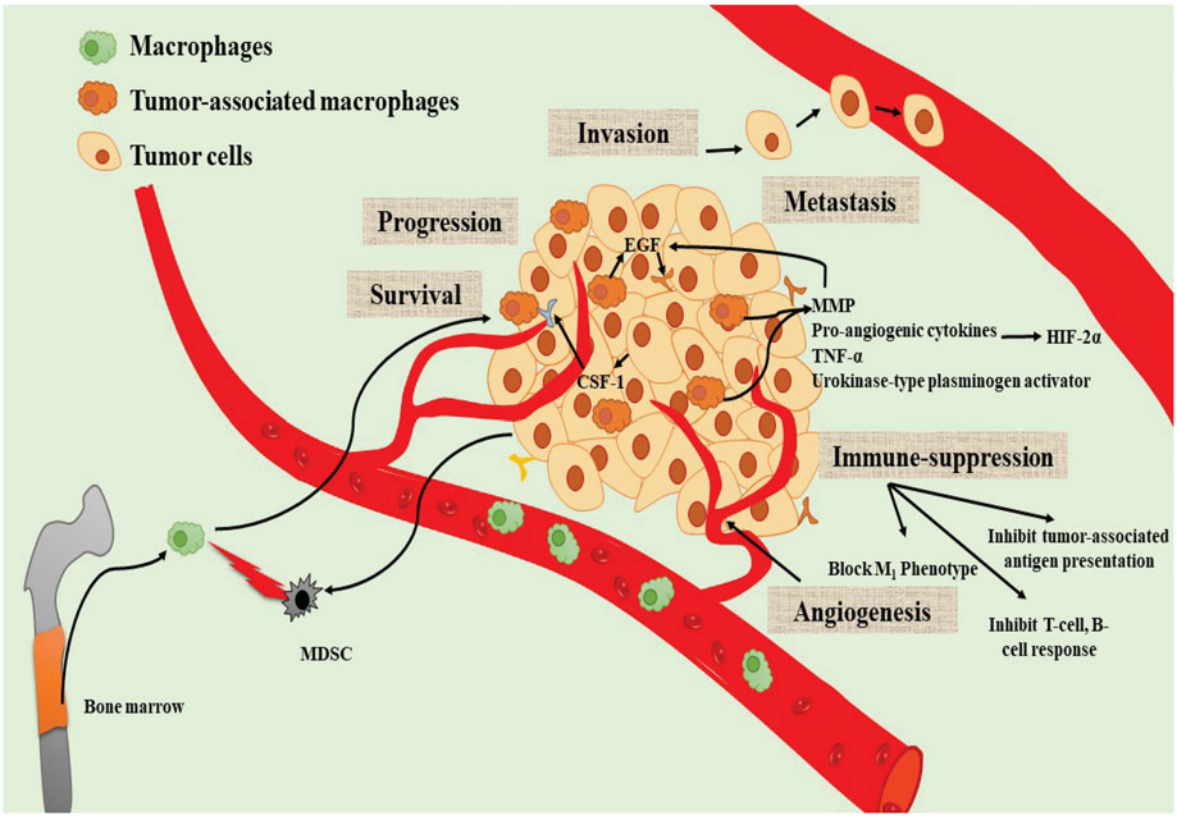

Figure 1. Representation of TAM associated progression and metastasis of tumour cells within the TME.

during the interaction between TAMs and SCLC cells [50]. Additionally, programmed cell death protein-1 (PD-1), an immune-checkpoint drug target, is expressed in the TME and participates in the immunity of tumour cells [51]. PD-1 TAMs showed an M1-like surface profile, whereas an M2-like surface profile was observed with PD-1^{+} TAMs. Furthermore, the expression of PD-1 was found to increase proportionally with the time of engraftment and tumour volume in an experimental animal model. Therefore, blockade of the PD-1 response could result in inhibition of adaptive immune resistance in cancer cells [52]. A recent report on PD-1 blockade using a peptide, pembrolizumab, in NSCLC showed improved clinical benefits with progression-free survival [53].

Figure 1 shows representation of TAM associated progression and metastasis of tumour cells within the TME.

Therapeutic strategies for lung cancer treatment

In 2016, the United States National Cancer Institute established various techniques for the early identification and diagnosis of lung cancer stages. These techniques are utilised to decide the suitable treatment choices for each stage [54,55]. Surgery is the favoured initial option for treating early lung cancer; nevertheless, most lung cancer patients are diagnosed at late stages and hence chemotherapy alone, or in combination with other interventions is the first choice of treatment [55]. Despite advances in diagnostic techniques and the discovery of new chemotherapeutics, cisplatin and carboplatin are still used as a first-line agents for the treatment of lung cancer [56]. Other chemotherapeutics agents include docetaxel (DTX), paclitaxel (PTX), gemcitabine and premetrexed [55]. Two significant clinical challenges are associated with platinum therapy; high systemic toxicity and rapid acquisition of multidrug resistance (MDR), especially in NSCLC [57]. Although there have been improvements in diagnosis and treatment, the prognosis of lung cancer patients remains poor. Physiological and pathological barriers of the lung including the TME, which varies among individuals and types of cancer, are the biggest hurdles in treating lung cancer [58]. Recently, there has been significant progress in targeting TAMs to develop novel anti-tumoral therapeutic strategies, with encouraging results. These strategies include repressing the survival of TAMs, inhibiting the recruitment and activation of monocyte-derived macrophage, suppressing the tumour-promoting effect of M2-like TAMs, and enhancing the anti-tumour effect of M1-like TAMs [59]. Preclinical and clinical evidence suggests that TAMs are predominantly of the M2 phenotype that supports immunosuppression, cellular invasion, angiogenesis, metastasis and therapeutic resistance. Thus, repolarisation from the M2-like subtype to a M1-like subtype, or preventing M2 polarisation of TAMs in the stromal environment are potential targets against progression and metastasis of lung cancer [60]. Lung cancer treatments are associated with an extensive drug development process, exorbitant cost, high regulatory hurdles and shocking failure rates [44]. These problems may relate to the lack of successful first-line anti-cancer drugs, the development of drug resistance and non-optimal routes of administration [55]. There is a need for effective therapeutic agents and drug delivery carriers, which can reach to the TME and successfully deliver therapeutic agents to lung cancers. Hence, many lung delivery methods have been investigated to enhance therapeutic responses while reducing side effects. Figure 2 represents utilisation of therapeutic agents and engineered nanoparticles to reach and re-educate TAMs by repolarisation the tumour-promoting M2-like phenotype to the tumour-suppressing M1 phenotype.

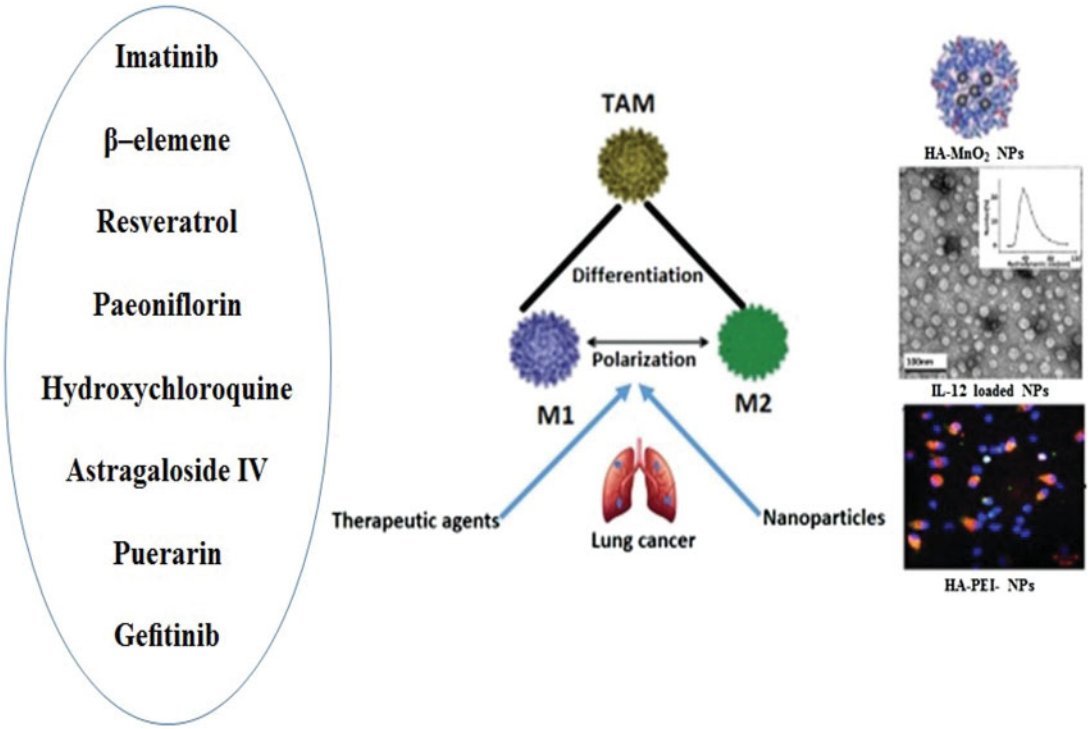

Figure 2. Represent utilisation of therapeutic agents and engineered nanoparticles to reach and re-educate TAM by repolarisation of M2 phenotype, which are tumour, promotor to M1 phenotype, which enables tumour suppression.

Therapeutic agents

Imatinib

Imatinib is a tyrosine kinase inhibitor (TKI), which has an anti-cancer activity on numerous solid tumours. Its anti-cancer action is partly dependent on immune cells including T cells [61]. *In vitro* studies using Lewis Lung cancer (LLC) cells showed that imatinib averted M2-like polarisation initiated by IL-4 or IL-13; imatinib repressed STAT6 phosphorylation and nuclear translocation, resulting in the arrest of M2-like polarisation [14]. *In vivo*, the percentage of M2-like macrophages in tumour and lung tissues was reduced after one-week of imatinib administration. Taken together, these results indicate that imatinib restrains M2-like polarisation both in the cell line and in the in vivo animal model; this may contribute to its anti-metastatic action in lung cancer [14]. However, these studies used a single animal model of primary and metastatic lung cancer, and further exploration of imatinib using other metastatic models is required to confirm the potential application of imatinib in the treatment of lung cancer [14].

β-elemene

β-elemene, the active component of elemene, has anti-tumour activity in NSCLC [62]. However, there have been few studies on the effect of β-elemene on the TME. An investigation of the effect of β-elemene on macrophage polarisation showed that the migration and epithelial mesenchymal transition of lung cancer cells was elevated by M2 macrophage-conditioned medium and that these effects could be prevented by β-elemene. *In vitro* studies showed that β-elemene repolarised macrophages from M2 to M1, as evidenced by an increased expression of M1 phenotype markers (iNOS) and decreased expression of M2 phenotype markers (Arg-1). These results suggested that β-elemene in combination with other chemotherapy might improve the therapeutic outcome by regulating both lung cancer cells and macrophages [15]. The molecular mechanism of β-elemene in regulating the polarisation of macrophages remains to be determined.

Resveratrol

RES is a polyphenolic compound naturally found in red wines and grapes; it has pharmacological activities in diabetes, cardiovascular diseases and lung cancer [16,63]. RES exhibits anti-cancer activity by decreasing the release of cytokines such as TNF-α, IL-6 and IL-12 [16,64]. Human monocyte-derived macrophages (HMDMs) induced by tumour-conditioned medium showed M2 polarisation with increased levels of IL-10 and decreased levels of IL-12 and TNF-α (M1 marker); treatment with RES prevented these effects, with macrophages showing M1 polarisation [16]. *In vivo* studies showed RES to decrease the level of the M2 markers Arg-1, IL-10 and CD206 in LLC tumour tissues. RES significantly decreased STAT3 activation and F4/80 positive macrophages in the tumour. These results suggested that RES can effectively suppress tumour growth by suppressing the M2 phenotype of TAMs, and may have a use in the treatment of lung cancer [16].

Paeoniflorin

PF, obtained from *Paeonia lactiflora Pallas*, inhibits lung cancer [65]. Many studies have reported that PF can inhibit the M2 macrophages in human colorectal carcinoma HT 29 cells [17] but there has been little work on its ability to reduce metastasis of lung cancer by inhibiting M2 macrophages. *In vitro* studies showed no effect of PF in inhibiting the growth of LLCs or peritoneal macrophages. However, *in vivo,* PF was shown to reduce the number of M2 macrophages in a subcutaneous xenograft tumour and to decrease lung metastasis on PF treatment. In LLC cells, PF

increased the proportion of the cell population in G0-G1 phases, while reducing the proportion of those in the S phase; there was a reduction in the M2 phenotype induced by IL-4. These results suggested that PF could inhibit lung metastasis of LLCs xenograft, at least partly through inhibiting M2 macrophages [17].

Hydroxychloroquine

HCQ has been widely studied as a chemo-sensitizer and an immune modulator in macrophages [18,66,67] but its effects in NSCLC remain unclear. The mechanism of HCQ in chemo-sensitisation and its effects on TAMs and CD8+ T cells have been studied *in vitro* and *in vivo* in combination with other chemotherapy for lung cancer treatment [18]. HCQ was shown to elevate the lysosome pH and inactivate P-gp in lysosomes to increase drug release into the nucleus for chemo-sensitisation, as well as to up-regulate inflammatory cytokines (Nos2, IL12b and IL6) and down-regulate immunosuppressive cytokines (Arg-1 and IL10) in TAMs; M2-TAMs were transformed into M1-like macrophages and CD8+ T cell infiltration was induced resulting in an anti-tumour effect [18]. These results suggest the therapeutic potential of HCQ for lung cancer treatment in the clinic.

Astragaloside IV

AS-IV, a natural saponin glycoside obtained from Astragali radix, was reported to have anti-oxidative, anti-inflammatory, immune-regulatory and anti-cancer effects [19,68,69]. Some studies have reported AS-IV to inhibit the lung invasion and metastasis of lung cancer [19,63,64]. *In vitro* and *in vivo* studies showed that the AS-IV inhibited M2 polarisation of macrophages as evidenced by the reduction in the CD206 marker and M2 associated genes; it also inhibited the invasion, migration, and angiogenesis of A549 and H1299 cells [19]. *In vivo,* AS-IV decreased tumour growth and the number of metastases of LLC, as well as reducing the percentage of M2 macrophages in tumour tissue by inhibiting the AMPK signalling pathway [19]. These findings suggest that the therapeutic potential of AS-IV for lung cancer treatment.

Puerarin

Puerarin, a flavonoid and the major bioactive ingredient isolated from the root of *Pueraria radix*, has been shown to have neuroprotective, anti-oxidant and anti-tumour properties on human lung carcinoma A549 cells [20]. It was found to inhibit tumour growth and metastasis in an NSCLC xenograft model, where it reduced M2 markers (CD206+, Arg-1+ and CD163+) and pro-tumour cytokines, while elevating M1 markers (CD197+, iNOS and CD40+) and enhancing the expression of anti-tumour cytokines as well as reducing the invasion and migration of NSCLC macrophages. The effects on M2 macrophage polarisation were associated with a partial inhibition of the MEK/ERK 1/2 pathway [20]. This study confirmed that puerarin is able to convert M2 to M1 phenotype, which is likely to accelerate its anti-tumour effects.

Gefitinib

Gefitinib, an EGFR TKI, has been approved for NSCLC metastasis. It was shown to inhibit the induction of cell apoptosis and to inhibit cell proliferation [21,70]. *In vitro* and *in vivo* data showed that gefitinib at a higher concentration (0.62 μmol/L) reduced the specific M2 genes expression (Mrc1, Ym1, Fizz1, Arg-1, IL-10 and CCL2) and M2 surface markers (CD206 and CD163) as well as inhibiting M2-like macrophage-mediated invasion and migration of LLC cells. Gefitinib inhibited IL-13-induced M2-like polarisation, specifically *via* inhibition of the STAT6 signalling pathway. These results demonstrated that gefitinib effectively inhibits M2-like polarisation both *in vitro* and *in vivo*, revealing a novel potential mechanism for the chemo-preventive effect of gefitinib against lung cancer [21].

Role of nanomedicine

In lung cancer treatment, there is an urgent requirement for innovative therapeutics to improve responses to regular chemotherapeutic agents, while reducing their side effects. Nanotechnology for cancer treatment has emerged recently; this makes use of minimally invasive administration routes and drug entrapment within nanoparticles to increase systemic circulation time, resulting in higher drug loading, while reducing non-target toxicities [59]. Owing to their small size, nanoparticles accumulate in defective tumour blood vessels and tend to show passive localisation of chemotherapeutic agents due to enhanced permeability and retention (EPR) effects, as well as utilisation of surface-functionalised active targeting; numerous products have gained clinical approval [71,72]. Several nanocarriers have been formulated to effectively transport chemotherapeutic agents into tumours with the aim of increasing retention of therapeutic molecules at the tumour site, while reducing their non-specific accumulation in normal tissues [71,72]. This has resulted in the FDA approval of several nanomedicine formulations such as albumin-bound PTX (Abraxane®), daunorubicin (DaunoXome®) and liposomes of doxorubicin (Doxil® or Caelyx®) [73]. Despite their underlying promise, the clinical benefits of these approved nanomedicines are still to be determined.

In recent years, there has been increasing interest in the relationship between nanomedicines and the TME [74]. TME modulation by approaches such as repolarisation of macrophages infiltrating the tumour environment, while leaving peripheral macrophages unharmed, is another option for treatment with reduced side effects, and may increase the usefulness of current chemotherapeutic agents [71]. Bisphosphonates modify the phenotypic status of TAMs to make them hostile to the tumour [71,75]. Zoledronic acid is a bisphosphonate whose anti-tumour action was restricted by its short half-life and rapid accumulation in bones. Polyethylene glycol coated nanoparticles of zoledronic acid were formulated to enhance its accumulation in the TME. *In vivo,* the drug *per se* had no anti-tumour activity, whereas the nanoformulations possessed anti-cancer activity and a reduction in the population of TAMs [71].

In situ oxygen generation inside tumours may be another effective method to induce TAM repolarisation to treat cancer [74]. For example, hyaluronic acid-coated manganese dioxide nanoparticles, which react with hydrogen peroxide in the TME to produce O_2, resulted in repolarisation of M2 to M1 phenotype [76,77]. Recent studies have confirmed the role of silver and gold NPs in the modulation of TAMs [78,79]. These studies showed that such NPs could increase the production of reactive nitrogen species (RNS) and reactive oxygen species (ROS) in tumours, leading to up-regulation of IL-12 and down-regulation of TNFα and IL-10, resulting in repolarisation of M2 to M1 phenotype [78,79]. Different phenotypes of TAMs influence the uptake of NPs and the growth of tumours. The uptake of silica NPs (less than 50 nm) was significantly higher for M2 as compared to M1 polarised HMDMs. *In vivo* findings also showed a higher uptake of silica NPs

by M2 as compared to M1 in animal model. However, larger particle such as microparticles (1.75 μm) showed no uptake by either phenotypes [80,81]. These investigations show the potential for specifically focussing on TAMs and M2 macrophages in creating tumour-targeted treatments. *In vitro* and *in vivo* data showed that carboxylated, multi-walled carbon nanotubes (MWCNTs-COOH) increased the expression of iNOS and CXCR10 (M1 markers), as well as TNF-α and IL-12 (Th1 cytokines), and reduced the expression of the M2 markers (CD206 and Arg-1). Additionally, the expression of the Th2 cytokines TGF-β and IL-10 was reduced, this being complemented by elevation of TLR-4 mRNA. MWCNTs-COOH converted IL-4/13-treated macrophages to the M1 phenotype and thus prevented the migration and invasion of LLC cells, this being accompanied by the upregulation of TLR-4/NF-κB p65 signalling. In conclusion, MWCNTs-COOH effectively prevents lung tumour metastasis by converting M2-polarised macrophages to M1 *via* activating TLR4/NF-κB signalling. Thus, MWCNTs-COOH provides a promising therapeutic approach against tumour metastasis by targeting TAMs [82].

Immunotherapy has shown potential in the treatment of solid tumours; nevertheless, the efficacy of treatment is restricted due to inadequate infiltration of immune cells into these tumours. The repolarisation of macrophages is an effective method to provoke an anti-tumour response [59]. Cytokines have been used in past for regulation of macrophages; however, their use is hampered by poor distribution and systemic side effects. One approach to resolve this is the use of nanoparticles. For example, poly-β-amino ester nanoparticles have been formulated to deliver interleukin 12 (IL-12) for re-educating TAMs [83]. *In vivo* these nanoparticles were found to decrease the fluorescent signals of CD206 and the m-RNA expression level of Arg-1 (markers for M2), but to increase the fluorescent signal of CCR7 and m-RNA expression level of iNOS (markers for M1) [83]. These results confirmed that the local reversal of TAMs *via* IL-12-loaded

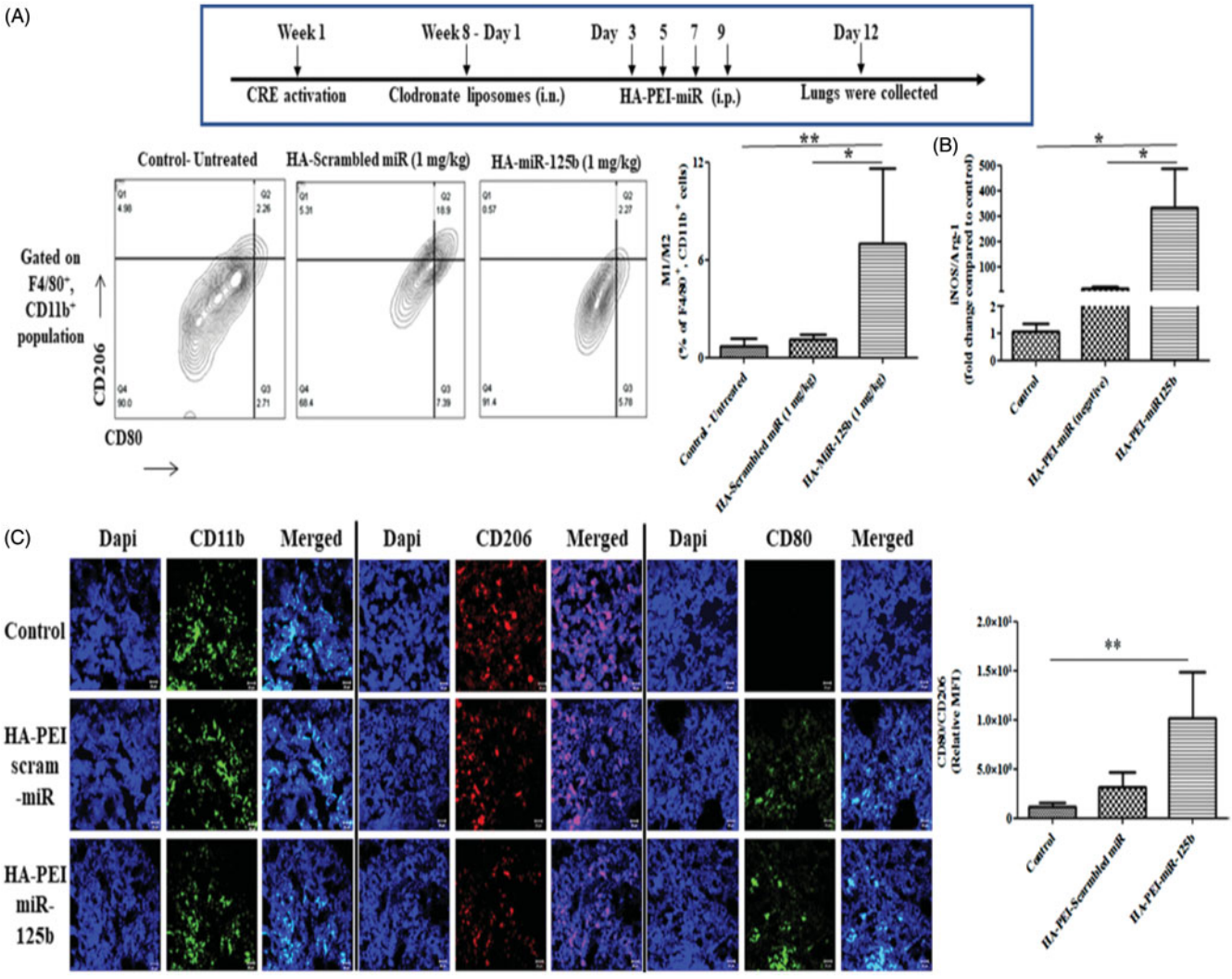

Figure 3. Represent repolarisation of TAMs following intraperitoneal administration of miR125b in hyaluronic acid poly (ethylene imine) (HA-PEI) nanoparticle formulations in the KRAS/p53 genetically engineered non-small cell lung tumour model. (A) Cells from homogenised lungs were stained for FACS analysis. Representative contour plots of CD206+ and CD80+ cells gated on the F4/80+ CD11b+ cell population. The ratio of CD80+/CD206+ cells gated on the F4/80+ CD11b+ cell population was plotted. (B) Cells from homogenised lungs were stained with F4/80 antibody for isolation using MACS magnetic beads, and RNA was extracted from these cells for expression of iNOS and Arg-1. The ratio of Inos/Arg-1 in IL-4 stimulated peritoneal macrophages treated with HA-PEI nanoformulations. qPCR was used for quantification of the gene expression level with β-actin as the internal control. (C) Lungs were isolated from mice on day 12, and immunohistochemistry was performed using confocal microscopy on lungs sections using CD11b, CD206 and CD80 antibodies. The ratio of relative mean fluorescence intensity (MFI) of CD80/CD206 in the HA-PEI-miR-125b group was compared to the control and HA-PEI-scrambled miR group; ($n = 6$) data are expressed as mean ± SD, and $^{*}p < .05$ compared to the control group (Reprinted from Ref. [72] with permission by Copyright holder ACS publication).

nanoparticles improves the therapeutic effects, achieving immunomodulation with negligible cytotoxicity. A few studies have shown that micro-RNAs (miR) can re-programme TAMs [84,85]. However, efficient and specific delivery of miRs to TAMs is challenging due to factors such as low permeability, and rapid degradation and clearance [86]. Parayath et al. prepared miR-125b encapsulated in hyaluronic acid (HA)-polye(thylene imine) (PEI)-based nanoparticles [85]. They showed that intraperitoneal administered HA-PEI nanoparticles repolarised TAMs in a mouse model of NSCLC, as evidenced by flow cytometry analysis, which demonstrated a decrease in CD206+ and an increase in CD80+ cells (Figure 3(A)). This finding was further validated by demonstrating a significant increase in the RNA expression of Arg-1 and an increase in the iNOS level in the nanoparticles-treated group (Figure 3(B,C)). Additionally, immunohistochemistry showed that HA-PEI-miR-125b-loaded nanoparticles produced a significant increase in the ratio of CD80/CD206 in compared with the control group. These combined results showed that nanoparticles are potential carriers to effect the repolarisation of M2 to M1 macrophages [85].

Conclusion and future perspective

TAMs are mostly found in the lung TME [58]. Multiple studies have indicates that TAMs are predominantly of the M2 phenotype in patients with NSCLC associated with lower survival rate [87]. More studies are required to determine the exact mechanisms underlying the polarisation of M1 and M2 macrophages, and to identify effective methods to increase the ratio of M1 to M2 phenotype to prevent tumour growth and recurrence [88]. Within the TME there is a variety of macrophages and there is a need to recognise more function-related macrophage markers which can be identified to individual macrophage phenotypes [79]. Strategies for modulating the TME should be designed to increase the diffusion of therapeutic agents and nanoparticles, thereby increasing the effectiveness of tumour targeting while avoiding the activation of metastasis. More focus is required on how to identify important differentiators of the M1 and M2 macrophages to target TAMs effectively [88]. Numerous therapeutic targets and drug candidates are being identified for the modulation of TAMs and these are rapidly moving towards clinical use both in combination with traditional therapeutics and with other immunomodulatory agents; therefore targeting TAMs is a promising strategy [89]. These highlights offer the opportunity to design highly selective and tailored drug delivery systems, especially nanomedicines, to further enhance therapeutic efficacy by increasing stability, improving pharmacokinetics, increasing selectivity, enhancing intracellular delivery and limiting systemic toxicity of existing chemotherapy agents in lung cancer [89]. Despite significant progress in nanomedicine delivery, multiple challenges need to be addressed to expedite the translation of nanomedicine to the clinic. The nanoparticles to be used for TAM targeting must be biocompatible and biodegradable and their formulation must be sufficiently reproducible and reliable for large-scale production [59]. Macrophages present in liver, lung and spleen are primarily responsible of the uptake of nanoparticles in the systemic circulation; thus, nanoengineering strategies such as surface modification of NPs, as well as anti-opsonising coating on NPs to avoid their uptake by mononuclear phagocytic macrophages, will facilitate uptake by the intended target cells. Further studies are required to understand the mechanisms underlying the interactions between nanomedicines and macrophages [59]. In conclusion, we believe that TAM targeting with therapeutic agents formulated into nanomedicines will enhance the efficacy of chemotherapy of lung cancer while reducing side effects.

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