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Macrophages directed approaches are paramount for effective cancer immunotherapies

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Abstract

Macrophages are double edge sword component of immunity and display phenotypical and functional plasticity which enable them to both promote and eliminate established tumors. Under the influence of immunosuppressive tumor microenvironment, tumor infiltrating iNOS+ and CD11b+ M-1 regulatory macrophages get polarized to Tumor associated macrophages (TAM) which are Ym-1 and Arginase+ iNOS- (M-2) and tropic to variety of tumors. Increased density of TAM in the variety of tumors has been correlated with poor prognosis which is due to their influence on angiogenesis and tissue re-modelling by which TAM support tumorigenesis as well metastasis. Apart from this, TAMs are also responsible for the maintenance of tumor microenvironment by their virtue of inducing endothelium anergy, which actually represent physical barrier for majority of cancer directed immune / chemotherapies. Therefore functional retuning of TAM to an M-1 phenotype is paramount for effective immunotherapy against established tumors which could be afforded by total body gamma irradiation in neoadjuvant settings or adoptive transfer of iNOS+ macrophages. In this review, we will discuss both existing as well future cancer directed immuno / adjuvant therapies targetting immunosuppresive tumor microenviorment particularly tumor-associated macrophages (TAM) for enhancing immunty against solid tumors (adenocarcinoma).

Introduction

After infections, cancer is next major cause of global morbidity and mortality and poses a significant thread on both patients and their families and the healthcare system as a whole. Available data indicate that the number of cancer-related deaths is more than those caused by AIDS, malaria, and tuberculosis combined; about one in four deaths is due to cancer. A major reason for this high mortality rate lies in resistant nature of variety of tumors against anti-cancer agents and bystander toxicity on healthy tissues and organs [1-4]. Cancer is caused by complex processes, which are directly linked to 'cell division', the fundamental process of life. Unlike normal cells that follow an orderly path of growth, division, and death, cancer cells continue to grow and divide continuously leading to aberrant cell mass which survive programmed death called 'Apoptosis'. According to their origin and location [5] cancers are classified into 200 types with varying degree of resistant against existing anti-cancer drug / therapies. Among various reasons, inefficient T cell migration is a major limitation [6] of cancer immunotherapy in general. Despite enough advancement was made in this field, none of the therapeutic intervention could prolong the survival of tumor patients beyond few weeks. This is mainly due to symbiotic association of tumor cells and tumor infiltrating macrophages (TAM) which drives sterile inflammatory response during the course of tumorigenesis. Various angiogenesis factors get accumulated at tumor site or within tumor microenvironment which serve as prognostic factors for cancer progression and renders tumor endothelium impermissive for immune cells infiltration. Though, many treatment options have been suggested / made over the past several decades, until today, no single treatment option is promising in controlling solid tumors like pancreatic and lung cancers.

Classical/Traditional treatment options

Depending on cancer type, tumor size and vasculature, so far three basic and fundamental approaches have been employed for cancer directed therapy and these are surgical resection of tumor, chemotherapy and radiotherapy. As relying on surgery is limited to early stage tumours, treatment options such as chemotherapy and radiotherapy are geared towards killing the cancer cells [7-10] themselves and are currently in use to date. However, these procedures are non-selective and have considerable clinical side effects. The hypoxic or anoxic micro-environment of solid tumour like adenocarcinoma poses a challenge to traditional cancer treatment [11-13] mainly due to increased angiogenesis of tumor. This predisposes tumour cells less susceptible to death by various chemotherapeutic drugs and / or radiotherapy which aimed to increased intratumoral oxygenation for killing by induction of apoptosis. Thus these do not represent good therapeutic options for the treatment of solid tumors cancer.

Alternative/Advanced treatment options

In recent years, various signalling pathways, which are important / decisive for tumor metabolism and growth, have been targeted by using pharmacological inhibitors for controlling the tumor growth [14]. Many genes like EGFR, p53, TRP53, PTEN, PI-3K XIAP, NF-kb and STAT3 have been identified and targeted [15-17] both chemically / genetically for controlling for rendering tumor cells sensitive for apoptosis. Though, in line with these, various anti-tumor agents and

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strategies were developed, mentioned in table 1, which extended survival of cancer patients significantly. However, due to genetic and / or epigenetic instability of cancer cells, no single compounds have been successful for breaking the resistance mechanisms to drugs.

Engineered nanoparticles based drug delivery

With significant advances in chemistry, biotechnology, nanotechnology, pharmacy, medicine, and imaging technologies, focus has been laid over a decade on developing efficient therapeutics that can selectively target the cancerous tissues while distinguishing malignant and benign cells, overcome biological barriers, and respond to the complex heterogeneous microenvironment inside a tumor for on-demand release of therapeutic agents in the optimal dosage range [18-22]. These include nanomedicines, magnetic nano-particles, bio-polymers like carbon materials, polymeric systems, and liposomes which are engineered, to meet the expectations of the current needs for effective cancer therapies [23-29]. Delivery of anticancer drugs through a nano-particle-based platform in comparison with traditional chemotherapeutics offers many advantage which include targeted delivery of drugs in a cell or tissues specific manner thus maximizing the treatment efficacy while alleviating systemic side effects, controlled release of drugs over a manageable period of time at precise doses, improved delivery of drugs that are poorly soluble in water, better protection of a drug from harsh environments such as highly acidic environment in the stomach, high levels of proteases or other enzymes in the blood stream before they can reach the targets thus leading to an extended plasma half-life of the drug in the systemic circulation, co-delivery of multiple types of drugs for combination therapy [23,30,31].

Antibody-drug conjugates (ADC)

ADCs are monoclonal antibodies (mAbs) attached to biologically active and highly potent cytotoxic drugs by chemical linkers to specifically bind tumour-associated target antigens [32-34]. The synergistic combination of mAbs conjugated to small-molecule chemotherapeutics, via a stable linker, has given rise to an extremely efficacious class of anti-cancer drugs. This unique combination of three components (mAb, linker and cytotoxin) to target tumor cells help in sensitive discrimination between healthy and diseased tissue while permitting greater control of drug pharmacokinetics. Currently two ADCs have been licensed, T-DM1 targets HER-2 [35,36] and brentuximab vedotin [37,38] and are already established their place in the category of most effective anti cancer drugs while several others are in pipeline.

Photodynamic therapy (PDT)

PDT**,** also called as *photoradiation therapy* or *photochemotherapy* is a promising alternative approach for improved cancer treatment [39]. A photosensitizer (PS; Porfimer sodium: most widely studied and used) which gets activated by light of a specific wavelength is administered causing selective damage to the tumor and its surrounding vasculature. The photosensitizing agent is either administered I.V. or S.C allowing the drug to be absorbed by the cancer cells with time. When light is applied to the area to be treated, the light causes the drug to react with oxygen forming a chemical that kills the cells mainly by inducing heat. PDT might also help by destroying the blood vessels that feed the cancer cells and by alerting the immune system to attack the cancer. It is less invasive than surgery, targeted, cost effective with no long-term side effects. PSs can be incorporated in nanostructured drug delivery systems such as liposomes, hydrogels, polymeric nanoparticles (PNP) improves the transcytosis of a PS across epithelial and endothelial barriers and afford the simultaneous co-delivery of two or more drugs. However, the success of PDT is limited mainly due to less invasive potential and their water insolubility.

Table 1. Existing Tumor directed therapies.

Treatment Type	Reference
Engineered Nanoparticle –based drug delivery	[23,24]
Antibody-drug conjugates	[23,34,108]
Immune Check-point Therapy	[46]
Photodynamic Therapy	[13,39,109]
PAMP based Cancer Therapy	[55,56,61,64]
Macrophage-Directed Cancer Immunotherapy	[64,65,90,91]
Stem Cell Transplant	[110-112]
Hyperthermia	[113-117]
Lasers in Cancer Treatment	[118,119]

Immunotherapy

It is well accepted globally that immune modulation is the pre-requisite for the effective therapy of both infections and cancer. This is due to the fact that cancer progression is a result of chronic inflammatory response which has both cellular as well as soluble components which are sufficient to eradicate cancer, if activated properly. Tumor cells driven immune editing or suppression is key factor which tumor cells take advantage off and exploit immune system in their favour. Therefore re-stimulation or readjusting host immune response is certainly believed to offer tremendous therapeutic advantage thus become paramount for effective treatment.

Targeting tumour microenvironment for cancer therapy

Tumor microenvironment *(TME)* is best defined as heterogeneous and symbiotic nitch of tumor cells, invaded immune cells (such as Treg, iNK and TAM) blood vessels, non-malignant cells mesenchymal cells and signalling molecules [40]. Other non-malignant cells include stromal cells, fibroblasts, pericytes, adipocytes which secrete growth factors and chemokines which not only promote tumor cells growth but also enhance angiogenesis and chemotaxis of immune cells into the TME [41]. A well-established tumor microenvironment is the result of dynamic equilibrium and symbiotic interactions of these cells [42] which is largely responsible for the development of tumor [41,43]. Therefore any tumor directed interventions targeting tumor microenvironment is anticipated to be more effective over other conventional treatment and afford improved clinical outcomes.

Immune check-point therapy

During malignancy, tumor cells both explore and exploit all possible way to suppress immune response against them because immune cells are the special cells which has the capacity of both eliminating as well as promoting malignancy depending on predominating signals prevailing within TME [44] known as immune check point which dictate immune cells to respond or not to any cellular entity. Out of various such check point listed in Table 2, upregulation of Cytotoxic T lymphocyte–associated antigen 4 (CTLA-4) and programmed cell death protein 1 pathway (PD-1), IDO and A2AR represent one of the best examples which have been well exploited by variety of tumor cells for hijacking host immune response during tumorigenesis [45-49]. Monoclonal antibody therapies directed against CTLA-4 and PD-1/ PD-1L has demonstrated some therapeutic advantage against variety of malignancies. ICOS and SOCS-1 represents another category of

Table 2. Current status of various immune check point inhibitors based approaches.

Potential Target	Agent (Inhibitory Receptors)	Stage of clinical development	References
CTLA-4	Ipilimumab Tremelimumab	Phase I/II/III/IV Phase I/II/III	[48,49,120]
PD-1	Nivolumab (MDX1106) Pembrolizumab (MK3475) Lambrolizumab Pidilizumab (CT-011) AMP-514 (MEDI0680; anti-PD-1)	Phase I/II/III/IV Phase I/II/III Phase I/II/III Phase I/II Phase I,II	[46,121-124]
PD-L1	BMS935559(MDX1105) MPDL3280A MEDI4736 MSB0010718C	Phase I Phase I Phase I Phase I	[125-129]
IDO	D-1MT INCB024360	Phase II Phase II	[130-133]
A2AR	SCH58261, SYN115	Phase I/II	[134-137]
TIM-3	Anti-TIMP3	Pre-clinical	[138-140]
LAG3	IMP321	Phase I/II/ III	[141,142]
KIR	Lirilumab (IPH2101) Nivolumab	Phase I/II Phase I	[143,144]

immune check points which negatively regulate TNF mediated tumor killing and support the developed of tolerogenic immune cells [50,51].

PAMP based cancer therapy

In both mouse and human tumor models, systemic activation of tissue-resident macrophages *in vivo* by either TLR ligands (mainly bacterial product) or CD40 stimulation [52-54] have been tried for effective anti-tumor immune response which is attributed to functional retuning of M2 TAM to M1 macrophages by such therapeutic interventions. Thus, such retuning may be paramount for effective cancer therapy in general and of cancer immunotherapy in particular. Several strains of bacteria like Clostridium spp. have capacity to selectively colonize in the hypoxic and necrotic areas of the tumour microenvironment [55-57] causing significant oncolysis. With the advent of biotechnology and bio-engineering, various strategies utilizing *Clostridium* are currently being investigated, enabling the delivery of therapeutics directly to the tumour *in situ*. In those lines, Clostridium-directed Antibody therapy (CDTA) where Clostridium is engineered to produce highly specific antibodies against tumour antigens is under use. One such approach was targeting HIF1α in tumour cells to control hypoxia and factors contributing to metastasis and invasion [58-61]. Another novel treatment option available is engineering *C. acetobutylicum* to express enzyme such as TNF-*α* that possess direct cytotoxic actions, as opposed to having pro-drug cleaving actions. The main mechanism by which bacterial derived product has shown promises against tumor cells is by their virtue of enhancing the release of TNF-*α* that is strongly anti tumor in nature , if produced in high doses where it functions as a vasculo-toxic agent [62]. Additionally, bacterial can be genetically engineered for multi enzyme effect that results in the release of tumour antigens from cells that have become necrotic, thus increasing the anti-tumour response by immune cells [63,64]. However, systemic activation of innate immune cells through bacterial product, sometime manifest severe systemic side effects limiting their use as safe option for clinical intervention.

Macrophage-directed cancer immunotherapy

Among various cells of immune system, like macrophages, neutrophiles, dendrites cells and natural killer cells, macrophages are double edged component and bear potential of both promoting cancer progression as well as rejection depending upon their phenotype they display. Macrophages are well known and integrated part of both innate and cellular immunity. Both peripheral and tissue macrophages together constitute the Reticulo-endothelium system which play major role in guiding tumor antigens for their establishment and metastasis as well as their effective eradication [65]. The presence of TAM at the tumor site represents one of the hallmarks of cancer-associated inflammation [66,67]. Normally tumors are infiltrated with leukocytes and their cross-talk with neoplastic tissues has shown profound effects on tumor progression or regression [65,68]. Phenotypic imbalance in M1/M2 effector phenotype during tumorigenesis is one of the major etiological factors which promote tumor growth by various mechanisms. For this point of view, M1 effector phenotype of macrophage thus represent the most suitable target cell populations for rendering tumor directed therapeutic interventions more effective. Histo-pathological analysis of several tumors revealed that around 50% of the tumor mass is composed of leukocyte among which T-lymphocytes and macrophages represent the major proportion [69-71]. The presence of these T cells within human tumors has been considered as an evidence of host immunity against tumor [72,73]. T lymphocytes have been found associated with a more favourable clinical outcome in colorectal, ovarian cancer, and melanoma. In contrast to T cells, macrophages is very well correlated in most – though not all – tumors with increased tumor angiogenesis, invasion, poor prognosis as well as several function of regulatory T cells [74-76]. Recent reports have demonstrated that various cytokines that are released from macrophages have tropic influence on tumors for their progression and metastasis [77-79]. The most pro-vital role of tumor associated macrophages by which they regulate the tumor micro-environment is to their potential to secrete plethora of cytokines/growth factors like VEGF-β, low concentrations of TNF-α, TGF-β, and Hypoxia Inducible Factor [65,80-84]. These secretions are most essential for the integrity of tumor microenvironment [85-89]. Therefore modulating the cytokine network between these tropical tumor associated macrophages and tumor cells could limit tumor progression would be the most effective immuno-therapy of the established and chronic tumor. Macrophages recruited into tissue react to variety of inflammatory and immune stimuli and attain differential phenotypes namely classically activated (M1), or alternatively activated (M2) macrophages as shown in Figure 1, thus reflecting the signals from the microenvironment they dwell in [90,91]. Classically activated macrophages are immunostimulatory with Th1-orienting properties while M2 are immunoregulatory with Th2 immune response [92]. Tumor polarized macrophages are referred as tumor-associated macrophage (TAM) [93,94], which exhibits several pro-tumoral functions, mentioned above [90,95]. TAM accumulation in majority of tumours and subsequent phenomenal changes being a major hurdle resulting in poor cancer prognosis, macrophage depletion, e.g. seems to one good therapeutic alternatives macrophage depletion using KO mouse (LySM cre, op/op mouse model) approaches or use of pharmacological drugs such as clodronate liposomes have shown to reduce tumor progression [96] & our unpublished data). Sessa et al have shown Trabectedin, a natural product derived from marine organism Ecteinascidia turbinate being specifically toxic to macrophages by affecting NF-Y, and KLF-2/4 transcription factors of major importance for mononuclear phagocyte differentiation thus other lymphocyte subsets in TME [97,98]. In similar lines, targeting TAM by acting on molecular pathways for TAM polarization such as NF-κB, STAT3 and HIF-1 which are considered to be the master regulators of TAM transcriptional programmes represent another potential therapeutic option. We have recently shown the therapeutic

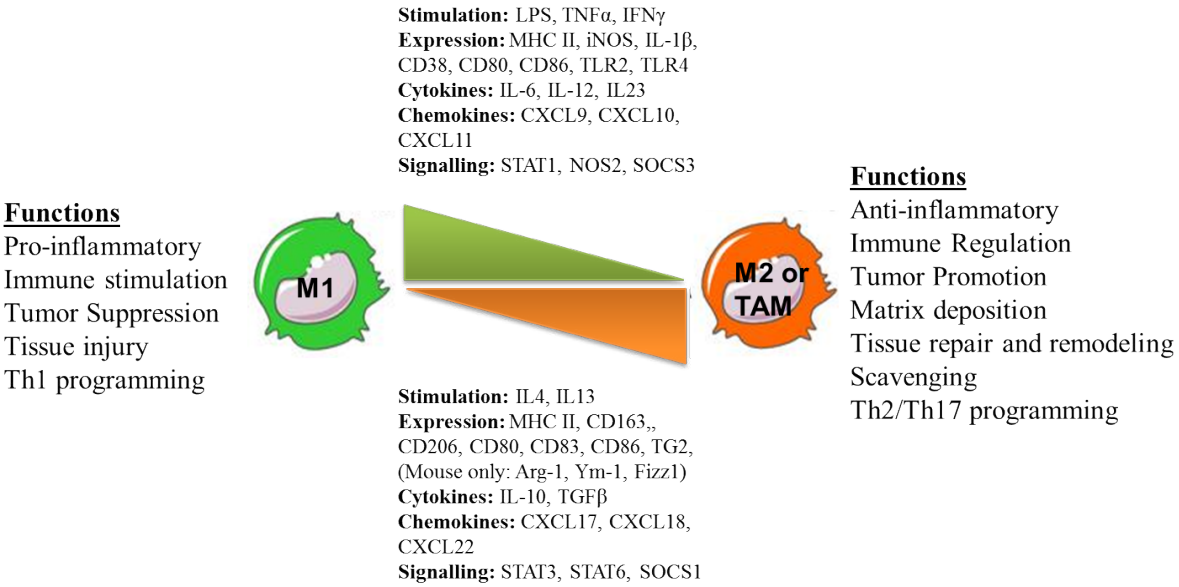

Figure 1. Schematic representation of phenotypic as well functional plasticity of macrophages. Macrophages are the special cells of host immune system, which, by their virtue of phenotypic plasticity can both control as well promote tumor growth thus represent key therapeutic target of current and future cancer immunotherapeutic interventions.

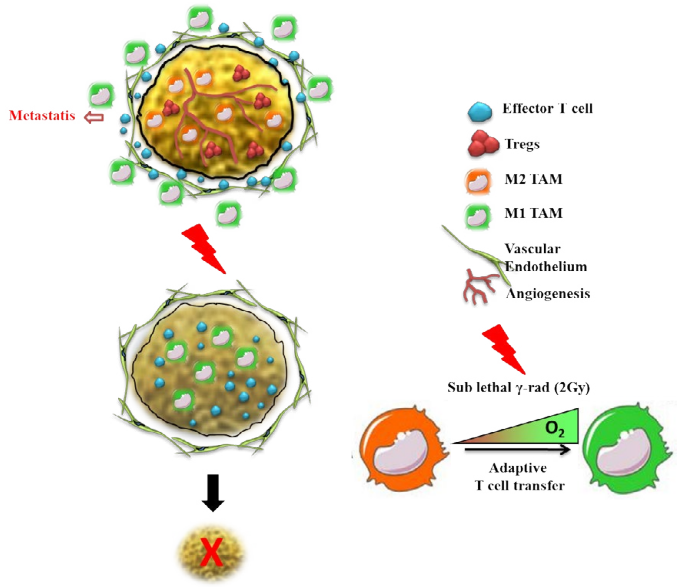

Figure 2. Tumor targeting by Low dose Radiotherapy. Low does radiotherapy potentially target tumor microenvironment mainly by functional retuning of TAM and unlocking endothelium anergy and support T cell based therapy for inducing tumor immune rejection of established tumor of pancreas and melanoma in therapeutic setting.

impact of low doses of gamma irradiation (LDI) in neo adjuvant setting as a potential non-invasive approach to improve cancer immunotherapy (a new feather in the traditional radiation therapy). Taking advantage of the fact that low dose of ionizing radiation activate immune cells including macrophages *in vivo* [99-103], we have recently shown that the potential impact of therapeutic radiation in skewing M1 repolarization of M2 subsets of macrophages within established tumours of pancreas [90,91] and demonstrated that LDI had an impact on tuning TAM M2 to M1 phenotype thus aiding in tumor directed T cell infiltration and subsequent tumour rejection in neuro-endocrine pancreatic tumour mice model (Figure 2). In similar lines, systemic irradiation also contributed for normalising tumor vasculature in a macrophage dependent manner [90]. Interestingly, single adoptive transfer of macrophages from systemically irradiated mice with LDI also resulted in enhanced cellular immunity in tumor bearing recipient mice in the absence of external radiation suggesting that systemic radiation with LDI is vital for macrophage retuning from M2 to M1 which is the current need of tumor directed therapies.

Mesenchymal cell therapy

Successful therapy against infection or tumor, should in principle, normalize tumor vasculature and overcome treatment related toxicities. To this end, tissue regeneration or homeostasis is critical for bringing body or tissue back to normal physiological status. This could be achieved by both subsiding inflammatory response and / or inducing cellular proliferation for replenishing tissue mass which is normally lost during various therapeutic regimens. MSC -based regenerative therapies have been introduced recently which function on their ability to differentiate into different mesenchymal lineages and to function as immunomodulatory / suppressive, angiogenic, anti-apoptotic, and proliferative agents [104,105]. Like TAM, MSC also secrete various factors which are involved in wound healing (VEGF, HGF etc.) as well as in immune suppression (PEG2, IDO) [106,107] and correlate with cancer progression, development, recurrence and metastasis. MSC has been instrumental in promoting cancer stem cell function or promoting tumor associated macrophages (TAM) function in tumor microenvironment. Therefore, an efficient strategy would be to engineer a different cell such as dermal fibroblast to promote MSC-like "immuno-privilege" devoid of associated secretory profile of the MSC for tissue regeneration post therapy.

Conclusion and future perspectives

These studies potentially demonstrate the significance of macrophage directed therapies in controlling tumor burden. On the basis of this, it is believed that changing of macrophages phenotype may improve or escort current tumor directed interventions which are facing therapeutic challenges in clinics. Management of M1/M2

imbalance is also believed to key also to minimize the risk of having cancer by chronic and persistent infection with intracellular pathogens like *Chlamydia* sp., *Mycobacteria* sp., *H. pylori* and others which, like tumor, also exploit Macrophage polarization for cancer development.

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