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The Polarization of Tumor-Associated Macrophages as an Effective Therapeutic Strategy: A Comprehensive Analysis

Aryan Kadali[1], Prahlad Parajuli[#], Jothsna Kethar[#] and Virgel Torremocha[#]

[#]Advisor

ABSTRACT

The complex interplay between tumors and their microenvironment presents challenges in cancer therapy, sparking interest in novel immunotherapeutic strategies. Current therapeutic approaches lack consistency and pose significant risks to patients. Tumor-associated macrophages (TAMs) play a pivotal role in tumor progression or inhibition, depending on their polarization state. This comprehensive analysis explores the potential of selectively repolarizing TAMs towards an anti-tumor phenotype as an effective therapeutic strategy. Nanoparticle-based delivery systems, such as polymeric, lipid-based, and inorganic nanoparticles, offer promising TAM targeting and repolarization avenues. These strategies demonstrate the ability to shift TAMs from a pro-tumoral M2 phenotype to an anti-tumoral M1 phenotype, resulting in significant anti-tumor effects. These processes have been both in vivo and in vitro, depending on the progress of the process. Nanoparticles, for example, have primarily been in vitro, but some have reached the in vivo stage. Despite the complexity of tumor immunology, the repolarization of TAMs emerges as a promising and versatile immunotherapeutic approach with reduced adverse effects compared to traditional treatments. This study underscores the importance of continued research and development in TAM repolarization, paving the way for future advancements and improved cancer therapies.

Introduction

In recent years, the complex relationship between the tumor and its microenvironment has emerged as a focal point in cancer research, revealing new avenues for therapeutic intervention. The tumor microenvironment (TME) includes various types of infiltrating immune cells, fibroblasts, blood vessels, and extracellular matrix proteins. Tumor-associated macrophages (TAMs) comprise a vital component of the immune infiltrate within the TME and have drawn considerable attention due to their dual role in promoting tumor progression or eliciting anti-tumor responses. This difference stems from the remarkable plasticity of TAMs, which can adopt distinct polarization states based on the local milieu. Amidst this landscape, a promising approach has suggested that selectively polarizing TAMs towards an anti-tumor phenotype holds hope as an effective therapeutic strategy. This study delves into this newer immunotherapy approach of repolarizing TAMs using various strategies, their effectiveness, challenges, and opportunities for further improvement towards enhancing the quality of life and survival of patients with cancer.

On the global landscape, studies involving agonists in relation to polarizing TAMS were used. Researchers in India repolarized glioblastoma macrophage cells with a non-agonist, Dectin-1 ligand, encapsulating an agonist fortoll-like receptor-9 (TLR-9). This combination was used to see if regenerative medicine could be used to fight against brain tumors. They were able to repolarize the TAMs resulting in the induction of high levels of inflammatory cytokines and oxidative bursts. The researchers concluded that the engineered nanoformulation could be a noteworthy therapeutic approach (Tiwari et al., 2021). Researchers from Germany and

Belgium conducted a study in which they injected the agonist IMDQ (imidazoquinoline), a ligand for the macrophage mannose receptor (MMR), into mice to activate TAMs. The intravenous injection led to a considerable decrease in tumor growth due to the repolarization of TAMs, which increased anti-tumor T-cell responses and a pro-inflammatory phenotype. Following the study, the researchers suggest that nanobody-drug conjugates can pave a path toward more effective macrophage immunotherapies (Bolli et al., 2021).

Within the national scale, specifically in the USA, experiments involving mice as well as clinical studies involving human patients have been conducted to test the effectiveness of TAM polarization in various tumors. Researchers based in Michigan and Wisconsin created a complex study that tested the anti-tumor effects of immunotherapy (IT) combined with multidrug chemotherapy (CT) in mice models. . In specific, the immunotherapy (IT) included monoclonal anti-CD40 agonist antibody + cytosine-phosphate-guanosine-containing oligodeoxynucleotide 1826 (CpG-ODN) immunotherapy (IT), which was integrated with a vincristine, cyclophosphamide, and doxorubicin-based multidrug chemotherapy (CT). The researchers gathered that the fusion of IT and CT led to notable anti-tumor effects in mice with established 9464D neuroblastoma or B16 melanoma (Buhtoiarov et al., 2011). Neuroblastoma is a common malignant tumor that affects the sympathetic nervous system (SNS), commonly in childhood, while melanoma is the most dangerous form of skin cancer. Researchers in Kentucky specifically investigated osteosarcoma (OS), a rare bone cancer that only had roughly 4000 new cases in 2022. The researchers acknowledged that many standard immunotherapies were not effective enough to be used to treat osteosarcoma (OS), leading to the heightened interest in polarization of TAMs within OS. Although they found promise in the strategy, they suggested a more thorough study of TAM polarization before a wide-scale implementation of the strategy (Anand et al., 2023).

This study addresses the pressing question of whether selectively polarizing TAMs towards an anti-tumor phenotype holds promise for effective therapeutic interventions. The urgency in conducting this comprehensive analysis lies in the potential of macrophage polarization to revolutionize cancer therapeutics, as shown by global and national research findings. The outcomes of this study have the ability to be at the forefront of new and effective immunotherapeutic strategies against various cancers, addressing an unmet need in current treatment options.

Methodology

Within the context of tumors and their significant impacts on individuals' lives, there has been a rise in the discovery/innovation and applications of new treatments, specifically within a promising option: polarizing TAMs. This research aims to come to a decision on whether or not polarizing TAMs is a viable immunotherapy strategy. Although there will not be a 100% success rate for years to come, the higher the success rate rises, the better. Clinicaltrials.gov was used in order to assess ongoing clinical studies involving polarizing TAMs and, if available, the outcomes of the experiments. Additionally, databases such as EBSCOhost and the National Library of Medicine hold various journals with information on ongoing findings and future directions of treatment from across the globe. These journal articles were analyzed to gather information with the intent of coming to a conclusive decision.

Major Cell Types within the Immune System and Their Role in the Body

When considering the polarization of TAMs, it is essential first to examine the system that facilitates the maintenance of homeostasis within the body including combating threats: the immune system. The immune system is the human body's defense mechanism against all threats, including cancer. The immune system is made up of innate and adaptive components. The innate immune system is the first-responder tasked with the removal of newly detected pathogens and neoplastic cells. The innate immune system classifies the pathogens and cells as

harmful based on the expression of broad-range molecular patterns and distress or danger signals. On the other hand, the adaptive immune system is a more specific targeted system. It specializes in triggering immune responses to previously encountered, specific antigens.

The innate and adaptive immune systems are the two main components of the immune system. The most notable cells within the innate immune system include dendritic cells, macrophages, neutrophils, and natural killer cells (NK). Common cells found in the adaptive immune system include B and T cells. Although those are the systems each of the cells are most commonly associated with, the adaptive and innate immune systems are not mutually exclusive. In fact, the innate immune cells initiate and shape the adaptive immune system. For example, dendritic cells are also critical in the adaptive immune system. Both immune components are essential in inducing an inflammatory immune response, which is dependent on the type of stimulus and the duration of exposure or the activation of the primary innate response (Kumar, 2021). However, at times, the immune systems have to combine their efforts. Neutrophils are the most prevalent of the cells in the innate immune system. They are an essential component in fighting against microbial infections. Neutrophils are commonly known as the first responders to inflammation, infection, and injury (Liu et al., 2023). Dendritic cells are professional antigen-presenting cells (APCs) within the innate immune system. They play a vital role in the activation of naive T cells by presenting antigen information. Dendritic cells have two forms. The immature form has a low expression of MHCII and co-stimulatory molecules, and the mature form has a high expression of co-stimulatory molecules MHCII. Similar to neutrophils, dendritic cells cause an increase in inflammation and angiogenesis (Wang et al., 2023; Moghaddam et al., 2022). Natural killer cells contribute as the surveillance method for the immune system and, like neutrophils, fight microbial infections. Natural killer cells have the ability to easily recognize and eliminate a variety of cells, such as neoplastic, virus-infected, and stressed cells. Macrophages are mononuclear cells and are crucial in the innate and adaptive immune system types as they act as a bridge between them. They contribute to resistance against pathogens and regulate homeostasis. Macrophages are major players in the inflammatory processes of the immune system. They are differentiated into two types of macrophages: proinflammatory responses (M1/classical) or anti-inflammatory (M2/alternative). Macrophages play a crucial role in wound healing by contributing in different ways in different stages of the process. They are involved in tissue repair and angiogenesis by releasing growth factors and cytokines that stimulate the proliferation and migration of fibroblasts (Li et al., 2023; Moghaddam et al., 2022). The adaptive immune system is mainly comprised of T lymphocytes and B lymphocytes. The T lymphocytes comprise four major subsets (TH1, TH2, TH17, and Treg) and play an important role in pathogenesis. TH1 is involved in cellular immunity, while TH2 is involved in humoral (antibody-mediated) immunity. TH17cells mediate the host defensive mechanisms in various infections. T regulatory cells (Treg) prevent destructive immunity in tissues and are suppressors of inflammatory immune responses in the immune system. B lymphocyte cells usually fight against infections by reducing antibodies (Moghaddam et al., 2022).

Major Immune Cell Types While Battling Tumors

The immune system is a major influence on the outcomes of cancers in the process of development. At first the immune system is able to fight and continue suppressing tumor growth, but at a point some tumors are able to overcome the immune system's efforts. There is enough evidence that the immune system has a critical role in stopping tumor growth. In those early stages, the immune system can function as an extrinsic tumor suppressor by either restraining tumor growth or even destroying tumors while they are developing. While fighting cancer in more advanced stages, the immune system can play a role in functioning as a tumor promoter by promoting tumor growth, facilitating cell transformations, and sculpting tumor cell immunogenicity, the ability to provoke an immune response (Gubin et al., 2014). The elimination phase is the first phase in which the immune system responds to a tumor. Both the innate and adaptive immune systems have the ability to detect and destroy tumors in early stages before they are clinically visible. Within the elimination phase, the innate and adaptive immune

systems assist each other by recognizing and eliminating malignant cells (Maffuid & Cao, 2023). Although cancer cells can prompt immune responses, tumors are able to escape the surveillance of the immune system. When the nascent tumor escapes immune attack and starts progressing, they polarize the immune response to a wound-healing type of response, which is actually beneficial for tumor growth. Neutrophils have garnered increased attention recently because of their role in the progression of cancer. Their role in cancer progression includes the promotion of angiogenesis, cancer metastasis, and immunosuppression (Moghaddam et al., 2022).When dendritic cells migrate from peripheral tissues to the tumor's microenvironment, they can undergo maturation and uptake tumor antigens. This migration can also be accompanied by increased fascin expression. Although high levels of fascin expression in normal tissue dendritic cells promotes different immune responses, high levels of fascin expression in intratumoral dendritic cells are associated with supporting tumor development. So, the right amount of fascin expression is beneficial in combating against tumors (Wang et al., 2023). Natural killer cells can kill tumor cells via various mechanisms, including receptor-ligand interactions. However, in rapidly progressing tumors, NK cells also become dysfunctional. This dysfunctionality renders the surveillance of natural killer cells ineffective (Wang & Wei, 2023; Moghaddam et al., 2022). The immune system faces challenges in detecting antigens because cancer cells express self-antigens. All somatic cells express self-antigens in the context of MHC Class I. The self-antigen expression inhibits an autoimmune response(s), an autoimmune response is an immune response in which the immune system mistakenly attacks healthy cells, organs, and tissues. When the self-antigens mutate, they are not viewed as 'self' anymore, causing T cells to recognize and kill them. Additionally, tumor cells acquire immune evasive strategies in order to escape a successful immune response. Due to the problems faced by the immune system, immunotherapy strategies such as TAM polarization have emerged (Thol et al., 2022). T cell subsets have the ability to promote the progression of tumors by producing cytokines and angiogenic factors. This, in turn, can increase inflammation and angiogenesis in the tumor microenvironment. In some cases, the antibodies produced by B cells react with the self-antigens and damage tissues (Moghaddam et al., 2022). The role of macrophages in battling tumors will be further explained in subsequent sections.

Macrophages and TAMs

To reiterate, macrophages are vital cells within the immune system. They are a versatile cell type and have the ability to respond to external stimuli and adapt to their respective surrounding environment. M1 macrophages release pro-inflammatory cytokines and produce preservative responses leading to antitumor and antimicrobial activity. The activation of M1 macrophages is induced by factors such as intracellular pathogens, bacterial cell wall components, lipoproteins, and cytokines. M2 macrophages are opposite to M1 macrophages in many ways. They release anti-inflammatory cytokines that support Th2-type immune responses and wound healing. M2 activation is induced by factors including fungal cells, parasites, immune complexes, and apoptotic cells (Anand et al., 2023; Rőszer, 2015). TAMs (tumor-associated macrophages) can be both M1 or M2 macrophages, but they are mostly M2 type.

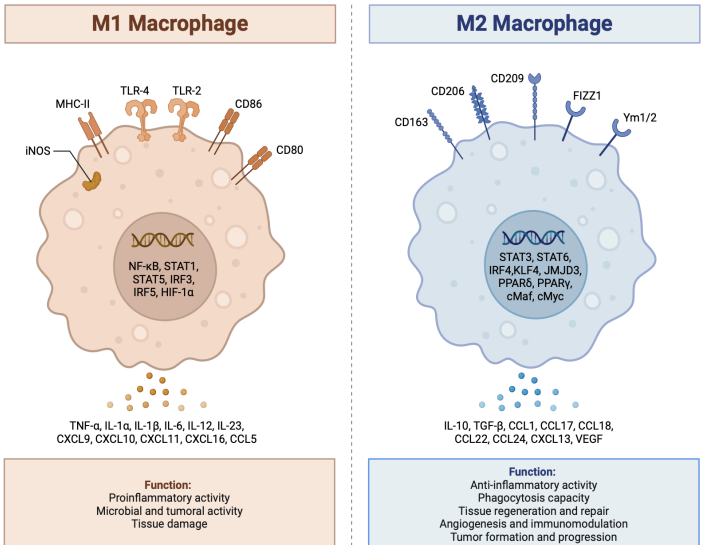

Figure 1. Diagram of M1 and M2 macrophages, including some of their simple functions. Created with BioRender.com

TAMs refer to the macrophages that come in contact with tumors, hence the name tumor-associated macrophages. Many macrophages orchestrate activities within the tumor microenvironment (TME). TheTME is the surrounding environment in which immune cells, blood vessels, bone-marrow derived inflammatory cells, fibroblasts, etc. exist. Tumor cells create growth factors and chemokines as a method of attracting macrophages and altering them to the M2 phenotype (Jahandideh et al., 2023). TAMs can either start as tissue resident macrophages or ones infiltrated from peripheral blood. The origin depends on factors such as the type of tumor, tissue involved, and the TME. In terms of inflammatory macrophages, the peripheral blood infiltrating macrophages tend to be more inflammatory as they are often associated with the M1-type macrophages. Tissue resident macrophages do not have as pronounced of a response compared to the infiltrating ones as they can exhibit either M1 or M2 type features. TAMs play a pivotal role in the formation and development of tumors. For instance, TAMs can provide growth factors that promote tumor's growth and angiogenesis. They can also assist with the promotion of invasion and migration of the tumor cells by degrading the extracellular matrix (ECM). Additionally, TAMs can secrete immunosuppressive factors to suppress anti-tumor immune response. These immunosuppressive factors are IL-10 and transforming growth factor β (TGF-β) (Feng et al., 2022).

Therapeutic Strategies to Repolarize TAM

Nanoparticles:

The use of nanotechnology is an emerging immunotherapy strategy. Advances in nanotechnology have the ability to improve human health and well-being. Applying nanomedicine strategies allows for the modulation of the surface of a delivery system toward cellular targeting. TAM-targeting nanoparticles have attracted much attention recently due to their potential in solid-tumor immunotherapy. The International Union of Pure and Applied Chemistry (IUPAC) defines any particle with submicron size as a nanoparticle. The nanometer size and other properties of nanoparticles offer biomedical fields many advantages. One of these advantages is the ability of the nanoparticles to increase load efficiency using their relatively high surface area in comparison to micro-scale particles. Another advantage is the tunable parameters of nanoparticles. The tunable parameters benefit both diagnosis and treatment with capabilities such as specific targeting, decreased systemic toxicity, and fine-tuned application. The last notable advantage of nanoparticles is the relatively stable structure that can

shield the cargo to prevent early degradation of the drugs. To target TAMs efficiently, nanoparticles should be tailored to have a larger size and pathogen-mimicking shape, which macrophages commonly phagocytose and capture. Currently, modifying nanomedicines with various ligands of some receptors that only certain peritumoral macrophages possess can leverage active targeting strategies. The most common of these receptors are scavenger receptors. Common ligands range from M2 peptides to mannose and folate. Various nanoplatforms can be classified into four distinct groups: polymeric nanoparticles, lipid-based nanocarriers, inorganic nanomaterials, and others (Shi and Gu, 2021).

Of nanoscale formulations, polymeric nanoparticles are one of the most significant that are linked by monomers with covalent bonds. Polymers can be engineered to have various forms, including polymeric micelles, polyplexes, and solid particles. Polymeric nanomaterials have several noteworthy advantages within biomedical usage. The first is the simple manufacturing technique. This can vary between self-assembly and emulsion fabrication processes. This provides the possibilities of off-shelf nanomedicines. Additionally, functional groups on the surface of polymeric nanomaterials enable modification to allow for specific targeting. These nanoparticles are relatively biocompatible and biodegradable. This is especially prevalent for natural polymers, including dextran, chitosan, and alginate. Other synthetic polymers are biologically safe. One of these synthetic polymers is polylactide (PLA). On top of this, the Food and Drug Administration (FDA) approved them for drug delivery and tissue engineering fields. Amino-modified and Carboxyl-modified polystyrene nanoparticles were able to suppress macrophages from polarizing towards the M2 phenotype with down-regulated expressions of CD200R, CD163, and IL-10, without affecting M1 markers in the macrophage (Ann-Kathrin Fuchs et al., 2016; Shi & Gu, 2021).

Another essential type of nanoparticle is lipid-based nanoparticles. Lipid-based nanoparticles are popular for their low immunogenicity, easy manufacturing scale enlargement, and high biocompatibility. These advantages allow lipid-based nanoparticles to serve as proper candidates for biomedical applications. Liposomes and lipid nanoemulsions are the two representative types of this nanoparticle class.

Inorganic nanomaterials are a class of nanoparticles defined as being composed of inanimate matters and commonly include metal matrixes. These metal matrixes have been found to include metals like calcium, iron, and gold or even nonmetals like silicon. Inorganic nanoparticles are able to stay stable for long periods of time and allow for stricter sterilization when compared to their organic counterparts. Even finer controllability is an option within inorganic materials. Some inorganic types even have the capability to reprogram macrophages by themselves. One such example is iron oxide nanoparticles. In fact, iron oxide nanoparticle ferumoxytol was found to inhibit tumor growth by polarizing macrophages towards the M1 direction (Shi and Gu, 2021).

Surface coating the nanoparticles mediates the active targeting and may improve drug delivery and the therapeutic effect. Additionally, it can lower side effects. Mannosylated drug delivery systems have been found to interact with macrophages through transmembrane receptors. The exploitation of drug-free delivery systems and their cellular interplay, such as immunomodulatory potential and macrophage activation, is still limited. However, the polarization of human THP-1-differentiated macrophages via drug-free fucoidan/chitosan nanoparticles functionalized with mannose or mannan was achieved. Both mannan-coating and mannose-coating carbohydrates led to classically activated macrophages, however, not with non-functional nanoparticles. Data shows that these drug-free nanoparticles have the ability to alter the macrophages' phenotype in vitro. Therefore, the data suggests the potential of drug-free nanoparticles as therapeutic tools for treating cancer or intracellular infections (Serrasqueiro et al., 2023).

Figure 1. Retrieved from EBSCOhost (Shi and Gu, 2021). This modified table represents various nanostrategies targeting TAM repolarization. In recent years, many nanoparticle strategies aimed to reprogram M2 type TAMs into the M1 counterparts have been developed, which include polymeric nanoparticles, lipid-based nanomedicines, inorganic nanoparticles, and others. After many of these nanocarriers were administered, the macrophages in the tumor microenvironment turned into the "friendlier" subtype (M1) and ultimately end up eliminating cancer cells with the assistance of other immune cells.

Main Matrix	Therapeutic Agent	Tumor Model
	Polymeric nanoparticles	
PLGA	Natural Killer cell membrane	4T1
PLGA	Iron oxide, M1 cell membrane	4T1
PLGA	CpG	B16F10
	Lipid-based nanoparticles	
Liposome	BLZ945, anti-CD206	4T1, B16F10
Liposome	BLZ-945, Selumetinib	4T1
	Inorganic nanoparticles	
Iron Oxide	Iron oxide, membrane blocking CD47-SIRPα	4T1, B16F10
Iron Oxide	Iron oxide	4T1
Iron Oxide	Iron oxide, hyaluronic acid	4T1
Iron Oxide	Iron oxide, poly (I:C)	B16F10
Iron Oxide	Iron oxide and hyaluronic acid stimulated macrophages	4T1

This data set was narrowed down after the top three most prevalent main matrixes and tumor models were identified. These were identified for the purpose of finding the most effective of these current combinations. Once identified, other nano strategies that did not include one of the most prevalent main matrixes and one of the most prevalent tumor models were removed from the table. These nano strategies were narrowed down in order to promote further investigation into these specific nano strategies, or perhaps other ones that were not included in this table in the first place.

Figure 2. Retrieved from EBSCOhost (Anand et al., 2023). Table represents drugs targeted against TAM/M2 macrophages using in vitro and in vivo studies. Within the tumor microenvironment, T cells can express PD-1, which can interact with its ligand PD-L1 on cancer cells as well as M2 macrophages, leading to the inactivation of T cell function. Ant-PD-1 or Anti-PD-L1 antibodies block their interaction, which causes the activation of T cells that prompt anti-cancer activity. The repolarization from M2 to M1 phenotype reduces the expression of PD-L1 in the tumor microenvironment. Various agents that can complete the mentioned polarization are in the process of being developed. Those agents which are under development as strategies to target macrophages are shown below.

Drug	Target Cell Type	Markers Used for Flow Cytometry/IHC/RT-PCR	Inhibition In Vitro Drug Concentration	Target Cells Type: In Vitro/Primary Tumor/Pulmonary Metastasis/In Vivo	Mechanism

All-Trans Retinoic Acid (ATRA)	TAM/M2	F4/80, CD206+ CD209. CD 86, CD 14	Pretreatment of mice for 7 days at 20 mg/kg and post injection 40 mg/kg for 4 weeks	ATRA reduced TAM macrophage polarization in vitro. Secondary lung microscopic metastatic reduction was seen to 60% and 95% after 1- and 2-weeks treatment respectively	MMP12 Inhibition from M2 macrophages to suppress metastasis
Asiaticoside (ATS)	M2	CD 206, CD14, CD86, Ki67, Bcl-2, Bax, VEGF	40 µM invitro and 10 mg/kg in vivo every 2nd day for 30 days	ATS restrained the M2 phenotype and helped reduce the tumor weight by 3-fold and suppressed OS progression	TRAF6/NF-kB inhibition
Graphene Oxide (GO) mediated Photothermal therapy (PTT)	M2	CD206, CD209, Arg-1	0.05/ mg/mL in vitro and 808 nm light (0.7 W/ cm^2, 1.5 min in vivo, temperature ≥ 45 C	Low temperature PPT helped polarize to M1 phenotype and show antitumor effects	Suppression of IL-2 induced M2 repolarization
Mifamurtide	M2	C9D11b, CD3, CD45.2, Ly6.G, MMP2/ MMP9, TNF-Ɣ, TRPV1	100 µM in vitro and 5 mg/mL in vivo	Treatment showed a reduction in osteoblast markers. M1 treated cells showed increased iron transporter expression of DMT1	Inhibition of STAT3 pathway / anti RANKL therapy
Pexidartinib (PLX3397)	TAM/M2	CD206, CD86, iNOS, IL-beta, CD80, CD206, CCL2	10 mmol/ L in vitro In vivo 5 and 10 mg/kg	Treatment showed suppression of TAM phenotype and increased chemotaxis. The mouse model showed suppressed primary and metastasis and possibility of transition into immunotherapy.	Inhibition of CSF1/ CSF1R signaling
Resiquimod cisplatin loaded	TAM/M2	CD86, CD206, CD44, CD62L	10 µg/mL	Treatment effectively suppressed the tumor growth in vivo and	D88-dependent signaling pathway

nanoparticle (CDDPNPR848)				stimulated the induction of immune memory response in spleen.	
Esculetin fraxetin	M2	Cyclin D1 and CDK4	In vitro- 10-100 μM In vivo- 3 or 10 mg/kg for 35 days	Esculetin showed cell cycle arrest at S phase and differentiation of M2 macrophages. Esculetin and fraxetin showed antitumor activity against primary and secondary metastatic cancer.	Inhibition of M2 macrophage differentiation

Discussion and Conclusion

Through different studies over the years, it was understood that tumors are a difficult condition to treat. There is no set cure for tumors yet, but developments in the field and advancements in technology have allowed for the future to look brighter. Those who experience tumors can expect better treatments and live longer lives. Current treatments for tumors include surgery, chemotherapy, radiation therapy, immunotherapy (IT), and hormone therapy. However, all of these treatments have some downside to the patient. The surgical removal of a tumor is not as precise as other treatments and shows high tumor resection rates. Radiation and chemotherapy can help in the removal of a tumor but can shorten one's life span and have shown other adverse effects. So considering this, many have turned to the direction ofIT. Examples of IT being used for tumor treatment are checkpoint inhibitors and CAR-T cell therapy. CAR-T cell therapy has found some success, but at the same time, relies on other factors for the efficiency of the treatment. Another immunotherapeutic strategy for treating tumors that has shown more promise is macrophage repolarization. In various studies, either in vitro or in vivo, nanoparticles and other drug treatments have shown success. Some of the benefits shown from these mentioned treatments other than repolarization include restraining the M2 phenotype, reducing the weight of the tumor, and other various antitumor effects.

With this research, it has become evident that macrophage repolarization has shown significant progress in treating tumors and deserves to continue to be investigated as a legitimate strategy. This study has shown the role of the immune system and its cells both during homeostasis and while battling tumors, how TAMs originate, and how TAMs can be dealt with either by drugs or nanoparticles. Examining these areas has allowed for confidence in the strategy and its future. In the future, more research and information regarding the strategy will continue to be released. More nanoparticles and drugs will be developed, allowing the strategy to be more versatile and beneficial to a greater number of people. Aside from the greater versatility of macrophage repolarization, these treatments have shown significantly lower adverse effects. Advancements in technology will allow this strategy to grow further with better and more efficient delivery systems. This research serves as part of the foundation for future studies, encouraging more breakthroughs with macrophage repolarization.

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