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Role of macrophage polarization in cancer progression and their association with COVID-19 severity

Abhimanyu Thakur [a,*], Rumpa Banerjee [b], Sudha Thakur [c], Gaurav Kumar [d], Shyam Sundar Thakur [e]

[a] *Ben May Department for Cancer Research, Pritzker School of Molecular Engineering, University of Chicago, IL, USA*
[b] *Eminent College of Pharmaceutical Technology, Barasat, Kolkata, India*
[c] *National Institute for Locomotor Disabilities (Divyangjan), Kolkata, India*
[d] *School of Basic and Applied Science, Galgotias University, Greater Noida 203201, India*
[e] *Ishwar Chandra Vidyanagar College, University of Calcutta, Kolkata, India*

ABSTRACT

Macrophages are a type of white blood cells that can exist in two different functional states, known as M1 and M2. M1 macrophages secrete pro-inflammatory cytokines that can promote tumor growth and metastasis, whereas M2 macrophages secrete anti-inflammatory cytokines that can inhibit tumor progression. This phenomenon, referred to as macrophage polarization, has been implicated in the development and progression of cancer. Furthermore, macrophage polarization is currently being investigated in the context of COVID-19 severity. It is believed that M1 macrophages may contribute to the excessive inflammation observed in severe COVID-19 cases, while M2 macrophages may confer protection against the disease. Hence, comprehending the role of macrophage polarization in both cancer and COVID-19 has the potential to enhance treatment strategies for both conditions.

KEYWORDS

Cancer; COVID-19; Macrophage polarization; M1; M2

*Corresponding author: Abhimanyu Thakur
E-mail address: abithakur1211@gmail.com

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1. Introduction

Cancer is a group of diseases characterized by the uncontrolled growth and spread of abnormal cells. It is a leading cause of death worldwide, affecting both men and women. Cancer can develop in almost any part of the body, including the skin, lungs, bones, and digestive tract.[1] The causes of cancer are complex and not fully understood. However, certain factors are known to increase the risk of developing cancer, such as smoking, excessive sun exposure, aging, certain viruses and bacteria, genetic predisposition, and certain environmental factors.[2] The majority of lung cancers are caused by smoking, while excessive sun exposure is a major risk factor for skin cancer. The signs and symptoms of cancer vary depending on the type and location of cancer, but may include fatigue, weight loss, fever, and pain.[3] Early detection and diagnosis of cancer are crucial in improving outcomes and survival rates. Diagnostic tests for cancer may include imaging tests such as X-rays, MRI, or CT scans, blood tests, and biopsies.[4][5] The treatment for cancer depends on various factors such as the type and location of cancer, the stage of cancer, and the overall health of the patient. Treatment options may include surgery, chemotherapy, radiation therapy, and immunotherapy.[6] Although these treatments are often effective in treating cancer, they may also cause side effects such as fatigue, nausea, and hair loss. [7] The outlook for cancer depends on various factors such as the type and stage of cancer, the patient's age, and overall health. Some types of cancer have a high survival rate if treated early, while others may be more challenging to treat.[8] Prevention is the best way to reduce the risk of developing cancer. Several ways to reduce the risk include not smoking, avoiding excessive sun exposure, maintaining a healthy weight, consuming a healthy diet, regularly exercising, and undergoing regular cancer screenings.[9][10] Cancer is a complex and devastating disease, but research and advancements in treatment have made it possible to successfully treat many types of cancer. With early detection, diagnosis, and treatment, many people can lead longer and healthier lives. [11].

2. Role of tumor microenvironment in cancer progression

The tumor microenvironment is a complex and dynamic ecosystem consisting of cancer cells, non-cancerous cells from the surrounding tissue, and the extracellular matrix (ECM). It plays a significant role in the progression and development of cancer and has become a crucial area of research in the ongoing battle against this devastating disease.[12] At the cellular level, the tumor microenvironment is a complex composition of various cell types, such as cancer cells, stromal cells, immune cells, and endothelial cells. While cancer cells are the primary culprits responsible for the initiation and progression of tumors, the other cell types in the environment also play a pivotal role in tumor development and growth.[13] Stromal cells serve as the primary source of structural support for the tumor, providing essential nutrients, growth factors, and cytokines. Immune cells, on the other hand, play a crucial role in the defense against cancer cells, while endothelial cells form the vasculature essential for supplying the tumor with necessary nutrients.[14][15] The extracellular matrix (ECM) is a vital component of the tumor microenvironment, composed of a highly intricate network of proteins, carbohydrates, and other molecules that provide a scaffold for tumor cells to grow on, as well as a means of communication between different cell types. The ECM can also undergo remodeling to support the growth of cancer cells. For instance, the ECM can be altered to promote angiogenesis, which involves the formation of new blood vessels to provide the tumor with necessary nutrients and oxygen.[16] The tumor microenvironment plays a pivotal role in the progression of cancer. Cancer cells can interact with the normal cells of the microenvironment in various ways, such as through the secretion of

cytokines that can promote cell growth or the activation of oncogenes that can drive tumor growth.[17][18] Moreover, the tumor microenvironment can undergo changes that promote tumor progression, such as alterations in oxygen levels or the provision of a source of nutrients for the cancer cells. Additionally, the tumor microenvironment can be modified in ways that promote metastasis, or the spread of cancer cells to other parts of the body. Cancer cells can utilize the ECM to migrate from the primary tumor to other locations, as well as leverage the vasculature to reach distant sites. Besides, cancer cells can interact with the immune system to evade detection and spread to other areas.[19] The tumor microenvironment is a vital component of cancer progression and a crucial area of research in combating this debilitating disease. By comprehending the intricate interactions among the different cell types within the tumor microenvironment, researchers can develop methods to disrupt the tumor microenvironment and halt tumor progression. Furthermore, comprehending how the tumor microenvironment can facilitate metastasis can lead to innovative treatments that can prevent the spread of cancer cells to other parts of the body.[20][21].

3. Association between cancer and COVID-19 severity

The relationship between cancer and COVID-19 severity is a complex and expanding research area. The focus is on identifying which cancer patients are at a higher risk of experiencing severe symptoms, hospitalization, and even death from the virus. It is apparent that the more advanced the cancer, the higher the risk of severe COVID-19.[22] Cancer is a systemic disease, indicating that it affects the entire body. Therefore, cancer patients have a compromised immune system, making them more susceptible to viruses like COVID-19. Cancer treatments, such as chemotherapy, radiotherapy, and immunotherapy, can further weaken the immune system, amplifying the risk of severe symptoms.[23] Moreover, a significant number of cancer patients are elderly and have chronic conditions, both of which can elevate the risk of severe COVID-19. The mechanism by which cancer heightens the risk of severe COVID-19 is under investigation. One theory is that the virus can cause inflammation and oxidative stress in the body, exacerbating symptoms and making them more severe.[24][25] The relationship between cancer and COVID-19 severity is a multifaceted and rapidly evolving field of study. Cancer is a systemic disease that can weaken the immune system, making cancer patients more susceptible to infections such as COVID-19. Cancer treatments such as chemotherapy, radiotherapy, and immunotherapy can further weaken the immune system, compounding the risk of severe symptoms. Furthermore, many cancer patients are elderly and have comorbidities, which also increase their risk of severe COVID-19. Several theories have been proposed to explain the link between cancer and COVID-19 severity. One theory suggests that the virus can cause inflammation and oxidative stress, which can exacerbate symptoms and worsen outcomes. Another theory proposes that cancer cells themselves may be more vulnerable to infection, leading to more severe disease in these patients. Research has shown that certain types of cancer are associated with an increased risk of severe COVID-19, including solid tumors such as those in the lungs, breast, and colon, as well as leukemia, lymphoma, and multiple myeloma. Specific treatments such as immunotherapy and systemic treatments like chemotherapy and radiotherapy can also increase the risk of severe COVID-19. It is crucial for clinicians to identify cancer patients who are at a higher risk of severe COVID-19 to provide appropriate care and make informed treatment decisions. By continuing to study the relationship between cancer and COVID-19, researchers can develop strategies to reduce the risk of severe disease in these vulnerable patients.[26] It is also crucial for researchers to investigate the association between cancer and COVID-19 severity, as it can provide valuable insights into the mechanisms of the virus and its interactions with cancer cells. As research progresses, more information will become available on which cancer patients are at a higher risk of experiencing severe COVID-19 symptoms. This knowledge will not only help clinicians in making treatment decisions and providing optimal

care for their patients, but also aid in the development of more effective and targeted therapies to combat COVID-19 in cancer patients.

4. Role of macrophage polarization in cancer progression

Macrophage polarization is a differentiation process that splits macrophages into two distinct subsets: M1 and M2 (Figure 1). M1 macrophages, also known as "classically activated" macrophages, play a critical role in pathogen recognition and destruction and are identified by their expression of pro-inflammatory cytokines such as interleukin-1 beta (IL-1β).[27] M2 macrophages, also known as "alternatively activated" macrophages, play a crucial role in wound healing and tissue repair. They are characterized by the expression of anti-inflammatory cytokines such as interleukin-10 (IL-10). In contrast, M1 macrophages, often referred to as "classically activated" macrophages, are involved in the recognition and destruction of pathogens and are characterized by the expression of pro-inflammatory cytokines such as interleukin-1 beta (IL-1β).[28] The role of macrophage polarization in cancer progression has been extensively studied. It has been found that the M1 phenotype is generally associated with an increased risk of cancer progression, as M1 macrophages produce pro-inflammatory cytokines that can promote tumor growth and metastasis. Moreover, M1 macrophages can also produce reactive oxygen species, which can damage tumor cells and induce apoptosis, thus aiding in tumor control.[29] Macrophage polarization plays a crucial role in cancer progression and the immune response to cancer. Studies have shown that the M1 phenotype is associated with an increased risk of cancer progression, as M1 macrophages produce pro-inflammatory cytokines that can promote tumor growth and metastasis. Additionally, M1 macrophages can produce reactive oxygen species that can damage tumor cells and induce apoptosis. In contrast, M2 macrophages are associated with a decreased risk of cancer progression, as they produce anti-inflammatory cytokines that can inhibit tumor growth and metastasis. M2 macrophages can also promote angiogenesis and tissue repair, which can help to suppress tumor growth. Furthermore, M1 macrophages can recruit other immune cells to the tumor site by producing pro-inflammatory cytokines, which can initiate an anti-tumor immune response.[30] The role of macrophage polarization in cancer progression has been extensively studied. Generally, it has been observed that M1 macrophages are associated with an increased risk of cancer progression due to their ability to produce pro-inflammatory cytokines that promote tumor growth and metastasis, as well as reactive oxygen species that can damage tumor cells and induce apoptosis. Conversely, M2 macrophages are generally linked to a decreased risk of cancer progression as they produce anti-inflammatory cytokines that can inhibit tumor growth and metastasis. Furthermore, M2 macrophages can promote angiogenesis and tissue repair, which can help suppress tumor growth. Apart from their role in cancer progression, macrophage polarization has also been found to be crucial in the immune response to cancer. M1 macrophages can produce pro-inflammatory cytokines that recruit other immune cells to the tumor site and initiate an anti-tumor immune response, while M2 macrophages can stimulate the differentiation of T-cells into effector cells that can recognize and destroy tumor cells. Finally, macrophage polarization has also been implicated in the development of drug resistance in cancer cells. M1 macrophages can promote drug resistance in cancer cells by producing pro-inflammatory cytokines, whereas M2 macrophages can suppress drug resistance by producing anti-inflammatory cytokines.[31] Overall, macrophage polarization plays a crucial role in cancer progression, immune response, and drug resistance. Understanding the mechanisms and functions of macrophage polarization in cancer can lead to the development of more effective treatments for cancer. It is essential to continue researching and exploring the complex interactions between macrophages and cancer cells to identify new therapeutic targets and strategies that can improve patient outcomes (Figure 2).

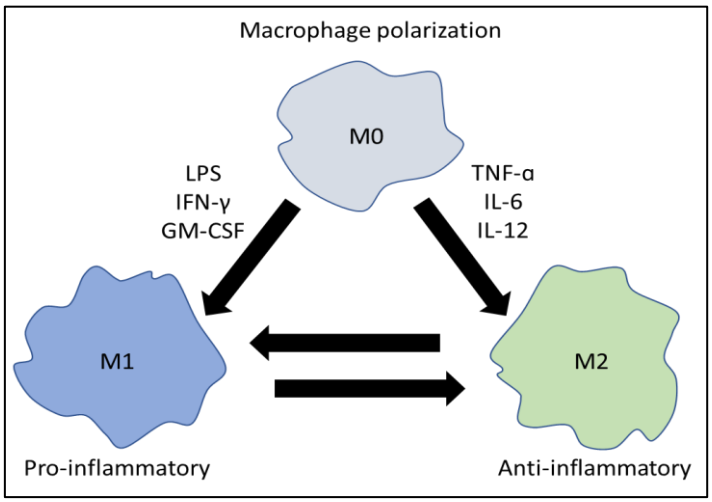

Figure 1. Polarization of macrophage. Macrophage cells exhibit a remarkable ability to adapt their behavior in response to the environmental cues they receive. This process, known as macrophage polarization, can entail a diverse range of changes, such as the activation of specific pathways and the adoption of distinct functional roles in the immune system's repertoire. By dynamically modulating their phenotype, macrophages can efficiently respond to diverse challenges and contribute to the maintenance of tissue homeostasis and host defense.

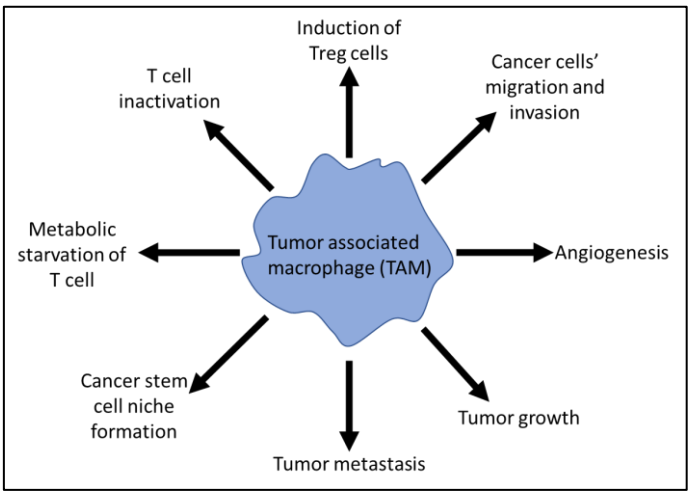

Figure 2. Role of tumor-associated macrophages (TAMs) in the process of tumorigenesis. Special markers and a range of factors secreted by tumor-associated macrophages (TAMs) have been shown to fuel the growth and spread of tumors. TAMs can significantly alter the tumor microenvironment, affecting various aspects of tumor progression. They can stimulate tumor cell proliferation, angiogenesis, and metastasis, while also triggering the production of cytokines that favor tumor growth and hinder the immune system's ability to fight the cancer. Indeed, TAMs have emerged as key contributors to the development and aggressiveness of numerous types of malignancies.

5. Role of macrophage polarization in COVID-19 severity

Macrophage polarization is a critical mechanism that influences the severity of the body's response to infection. In the context of COVID-19, macrophages are known to play a crucial role in the immune response of the body.[32] During infection, macrophages are a crucial component of the innate immune response, being recruited to the site of infection. Following recruitment, macrophages polarize into two distinct subsets, known as M1 and M2 macrophages. M1 macrophages produce pro-inflammatory molecules that activate the immune system and trigger

an inflammatory response, whereas M2 macrophages produce anti-inflammatory molecules that suppress the immune system and reduce inflammation. The balance between M1 and M2 macrophages is critical for controlling the severity of COVID-19, as an excessive pro-inflammatory response can lead to tissue damage and worsen disease outcomes.[33][34] The balance between M1 and M2 macrophages is crucial for regulating the body's response to COVID-19. When the balance is tipped towards M1 macrophages, the immune response becomes more intense, resulting in increased inflammation and a greater risk of complications. Conversely, if the balance tilts towards M2 macrophages, the immune response becomes less severe, resulting in decreased inflammation and a lower risk of complications.[35] Research has shown that in patients with severe COVID-19, there is a shift towards M1 macrophages, indicating that the pro-inflammatory response of the macrophages may contribute to the severity of the infection. Furthermore, studies suggest that drugs such as tocilizumab, which possess anti-inflammatory properties, could be effective in treating COVID-19 by rebalancing macrophage polarization towards M2 macrophages.[32] Overall, macrophage polarization is a critical factor that impacts the severity of COVID-19 infections. M1 macrophages, with their pro-inflammatory properties, have been found to be associated with more severe infections, while M2 macrophages, with their anti-inflammatory properties, are linked to milder infections. Therefore, a better understanding of how macrophage polarization contributes to the pathogenesis of COVID-19 may offer new insights into how to manage the disease more effectively (Figure 3).

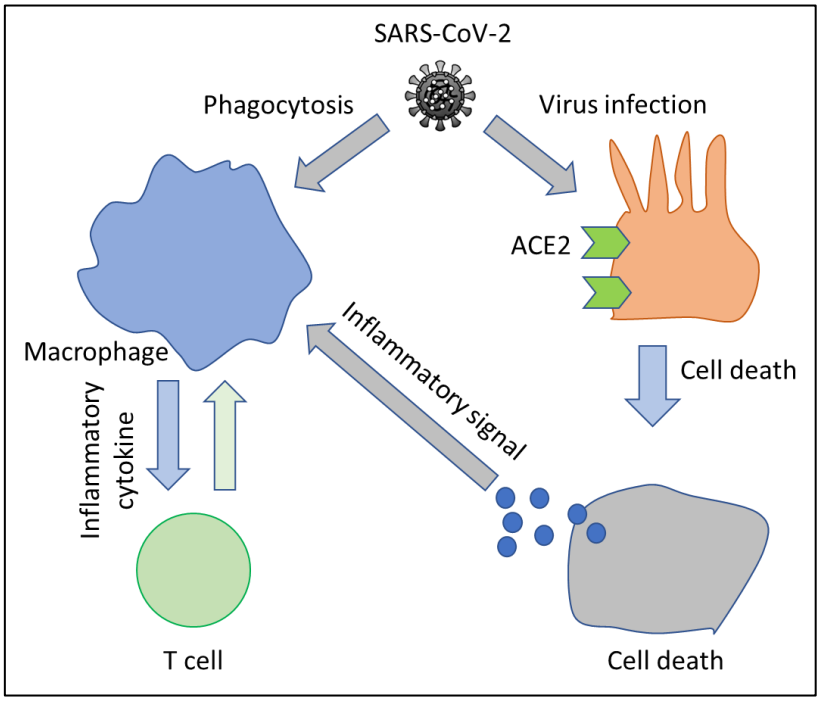

Figure 3. Activation of macrophage during COVID-19. Upon encountering SARS-CoV-2, macrophages become activated either through direct infection or by phagocytosing virus-infected cells, particularly pneumocytes. This triggers a cascade of responses, including the release of danger signals and pro-inflammatory cytokines, which can induce tissue damage and drive inflammation. T cells are then recruited to the site of infection, where they further stimulate macrophages and amplify the inflammatory response, leading to a synergistic increase in immune activation. This process can spread throughout the lungs and other organs, ultimately contributing to the systemic pathology seen in severe COVID-19 cases.

6. Advanced therapeutic approaches for cancer via targeting macrophage

Advanced therapeutic approaches for cancer strive to enhance current treatment options and develop novel,

more efficient methods to treat and manage cancer.[36][37] Immunotherapy has emerged as one of the most promising advanced therapeutic approaches for cancer, with the potential to provide new and effective ways to treat and manage the disease. By leveraging the body's own immune system, immunotherapy enhances its ability to recognize and destroy cancer cells. This can be achieved through various methods, such as monoclonal antibodies that specifically target and destroy cancer cells, or adoptive cell transfer, which involves transferring immune cells from one person to another to enhance the body's immune response.[38] Immunotherapy stands out as one of the most promising advanced therapeutic approaches for cancer. It harnesses the body's own immune system to combat cancer by enhancing its ability to detect and destroy cancer cells. Monoclonal antibodies are one type of immunotherapy that involves using proteins to specifically target and eliminate cancer cells. Another type, adoptive cell transfer, entails transferring immune cells from one person to another. Immunotherapy has been shown to be effective in treating various types of cancer, including lymphomas and melanomas.[39] In addition, gene therapy offers a promising approach for treating cancer by using genetic material, such as DNA or RNA, to modify or replace a gene that is causing the cancer. For instance, introducing a healthy version of a mutated gene can help the body combat the cancer. Targeted therapy, on the other hand, involves the use of drugs that specifically target molecules involved in the growth and spread of cancer cells. Unlike chemotherapy, which is a more generalized approach, targeted therapies can be tailored to a patient's specific molecular profile. Examples of targeted therapies include tyrosine kinase inhibitors, which target proteins that promote cancer cell growth, as well as monoclonal antibodies, which target specific molecules on the surface of cancer cells.[40] Advanced therapeutic approaches for cancer, such as immunotherapy, gene therapy, targeted therapy, and stem cell therapy, hold great promise for improving current treatments and providing more effective ways to manage cancer. Immunotherapy has proven effective in treating various types of cancer, including lymphomas and melanomas, by enhancing the immune system's ability to recognize and destroy cancer cells. Gene therapy aims to correct genetic defects that cause cancer by introducing healthy genes, and targeted therapy uses drugs to target specific molecules involved in cancer cell growth and spread. Stem cell therapy is being studied as a potential treatment for various types of cancer, including leukemia, lymphoma, and some solid tumors. These advanced therapeutic approaches offer hope to those living with cancer and have the potential to revolutionize cancer treatment and management.[41][42]

The treatment of cancer has undergone significant advancements in recent decades, with new therapies being developed each year. One of the most promising and advanced approaches is targeting macrophages to induce an immune response against cancer cells. This strategy involves modulating the activity of macrophages to enhance their anti-tumor properties, potentially leading to improved outcomes for cancer patients.[43] The use of macrophage-targeted therapy is an increasingly promising and advanced approach in cancer treatment. This strategy involves inducing an immune response against cancer cells by targeting macrophages, which play a key role in regulating the immune system. Monoclonal antibodies, cytokines, and other immunotherapies are some of the ways researchers are exploring to target macrophages. Monoclonal antibodies, for example, are synthetic antibodies created in a lab that can specifically target cancer cells. Cytokines are proteins that cells release to coordinate the immune response of the body.[44][45] The treatment of cancer has made significant advances in the past few decades, with new treatments being developed every year. One of the most promising and advanced therapeutic approaches for cancer is macrophage targeting. This approach aims to induce an immune response to fight cancer cells by using monoclonal antibodies, cytokines, and other types of immunotherapies. Monoclonal antibodies are artificial antibodies designed to target specific cancer cells, while cytokines help coordinate the immune response by activating macrophages to combat cancer cells. Other approaches to targeting macrophages include using small molecules to inhibit the growth of cancer cells and drugs that stimulate the production of macrophage-activating substances. Using these approaches has been shown to effectively reduce tumor size and prevent the spread of cancer. Targeting macrophages is a promising approach to treating cancer because it can be

used in combination with other treatments, such as chemotherapy and radiation therapy, to achieve a more comprehensive approach to treating cancer. This therapeutic approach has been used in the treatment of a variety of cancers, including melanoma, lymphoma, and breast cancer. Although this approach is still in its early stages, it is showing promise in the fight against cancer. By targeting macrophages, researchers can help the body's own immune system fight cancer cells more effectively, providing a more effective way to treat cancer and better outcomes for those affected.

7. Advanced therapeutic approaches for COVID-19 via targeting macrophage

Advanced therapeutic approaches for COVID-19 encompass a variety of treatments that aim to mitigate the severity of the virus, hasten symptom resolution, and mitigate the risk of long-term complications. These treatments are continually being developed and researched, and the approaches are rapidly evolving as more information is gathered. One promising type of advanced therapeutic approach for COVID-19 is antiviral therapy.[46] A range of antiviral medications have been tested, including remdesivir, favipiravir, and lopinavir-ritonavir. Although the effectiveness of these medications in reducing the severity of the virus varies, they are typically used in combination with other treatments to optimize outcomes.[47] Another promising therapeutic approach for COVID-19 is immunomodulatory therapy, which targets the body's immune response to the virus and modulates it to alleviate the severity of the disease. Various medications, such as corticosteroids, tocilizumab, and baricitinib, have been utilized in combination to achieve optimal efficacy. By regulating the immune system, immunomodulatory therapy can help prevent an excessive inflammatory response that may lead to serious complications.[48] Finally, monoclonal antibody therapies are being employed to treat severe cases of COVID-19. These therapies provide antibodies that can bind to the virus and limit its ability to cause infection. Monoclonal antibody therapies have been used in combination with other treatments to mitigate the severity of the virus and hold promise for long-term benefits.[49][50] Advanced therapeutic approaches for COVID-19 are continuously evolving as researchers work to develop new treatments that can reduce the severity of the virus, shorten recovery time, and minimize the risk of long-term complications. These approaches include antiviral therapy, immunomodulatory therapy, and monoclonal antibody therapy, among others. As more is learned about the virus and its effects on the body, these treatments are being refined and optimized to offer the best possible outcomes for those who contract the disease. With ongoing research and development, advanced therapeutic approaches for COVID-19 hold great promise for improving patient outcomes and reducing the impact of this global health crisis.

Advanced therapeutic approaches for COVID-19 that target macrophages are an emerging field of research. In the case of COVID-19, macrophages have been found to play a role in the pathogenesis of the disease. Targeting macrophages for COVID-19 therapy is a promising approach, which can be achieved through the use of drugs, antibodies, viruses, and manipulation of their metabolic pathways.[51][52] Various drugs and therapies have been developed to treat patients with COVID-19. For instance, remdesivir and favipiravir are drugs designed to target the viral enzymes of SARS-CoV-2 and have been found to be effective. Monoclonal antibodies have also been developed to block the virus from entering cells by targeting the spike protein of SARS-CoV-2. Additionally, engineered adenoviruses can stimulate an immune response against the virus by expressing SARS-CoV-2 antigens, which can reduce the severity of the disease.

Apart from drug-based therapies, macrophage-targeting therapies can also be used to modulate the immune system. Agents such as cytokines, small molecules, and antibodies can regulate the inflammatory response and slow down the progression of the disease. For example, cytokines like interferon can be used to inhibit the replication of the virus, while antibodies can be used to neutralize it. Small molecules like imatinib can also reduce the severity of the disease by inhibiting the activity of macrophages.[53][54] Overall, targeting macrophages with advanced therapeutic approaches is an emerging field of research in the treatment of COVID-19, with many promising

strategies being developed. These strategies hold the potential to improve outcomes for patients with COVID-19 and offer hope for more effective treatments for the disease.

8. Conclusions and future perspectives

Macrophage polarization plays a critical role in both cancer progression and the severity of COVID-19. In cancer, the tumor microenvironment regulates macrophage polarization, and pro-inflammatory M1 macrophages, along with anti-inflammatory M2 macrophages, contribute to tumor growth, invasion, and metastasis. By contrast, COVID-19 infection is linked to the presence of M2 macrophages, which increase the risk of severe disease and mortality. Targeting macrophage polarization is a potential therapeutic intervention for both cancer and COVID-19. Specific cytokines and drugs can be used to shift the balance between M1 and M2 macrophages, altering the immune response and improving patient outcomes. Checkpoint inhibitors and vaccines are also effective immune-targeting drugs that reduce the risk of tumor progression and improve outcomes in patients with cancer. Similarly, these drugs may help reduce the severity of COVID-19 and improve outcomes. Furthermore, vaccines prevent the activation of M1 and M2 macrophages in cancer and COVID-19, respectively. In conclusion, targeting macrophage polarization is a potential therapeutic strategy for both cancer and COVID-19. Research is needed to determine the best strategies and mechanisms underlying its role in cancer progression and COVID-19 severity. In the future, macrophage polarization targeting could effectively prevent and treat both diseases.

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Conflict of interest

The author claims that the manuscript is completely original. The author also declares no conflict of interest.

Author contributions

Conceptualization: Abhimanyu Thakur, Rumpa Banerjee, Sudha Thakur; Supervision: Gaurav Kumar, Shyam Sundar Thakur; Writing–original draft: Rumpa Banerjee; Writing – review & editing: Abhimanyu Thakur. All authors contributed to the article and approved the final manuscript.

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