HIGH SCHOOL EDITION
Journal of Student Research
Volume 13 Issue 4 (2024)

Overcoming Tumor Resistance: Targeting Stromal Components in Cancer Treatment

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ABSTRACT

The word “cancer” is still frightening to hear, despite the great improvement in cancer treatments and outcomes in recent years. Causing more than 10 million deaths annually, cancer stands as the second leading cause of death globally. Cancer is a generic term for many diseases that may impact any body part. While global oncology treatment strategies have improved, there has been a rise in cancer cases as a whole. Currently, most antitumor therapies target and eliminate cancer cells, and are not designed to affect the tumor stroma directly. Tumor recurrence can result from the interactions of the tumor stroma with both cancer cells and anticancer therapies. This research paper explores the relationship between cancer cells and the tumor stroma by evaluating the effectiveness of current cancer therapies alongside stromal-targeted treatments. The stroma promotes tumor growth through its interactions with the cancer cells, leading to resistance from traditional therapies. The tumor stroma can lead to reduced effectiveness of cancer therapy strategies through its various components. Therefore, proposed solutions should not only target cancer cells but aim to disrupt the stroma’s support or develop it into a tumor-repressive state. Addressing both cancer cells and the stromal environment may improve treatment effectiveness and reduce the likelihood of tumor relapse.

Introduction

Despite the increased development of cancer treatment strategies, a lack of effectiveness remains a problem. Cancer is a disease identified by uncontrollable cell growth caused by abnormal genetic conditions causing apoptosis to be unregulated. If untreated, it can disrupt essential bodily functions and spread to other parts of the body. Traditional anticancer therapies primarily target all rapidly dividing cells (Chemotherapy and Radiation therapy), while ignoring the surrounding components of the tumor, or tumor microenvironment (TME). However, being part of the TME, the tumor stroma plays an important role in the development of cancer and is proven to impact tumorigenesis, cancer progression, metastasis, and therapy resistance. Therefore, future research on cancer therapies targeting the tumor-promoting properties of the stroma is essential for achieving an effective long-lasting response (Valkenburg et al., 2018).

Cancer remains a global health issue, with cases and cancer-related deaths increasing yearly. According to the World Health Organization (WHO), by 2040, the world may see more than 28.9 million new cases and 16.2 million deaths a year. Research has identified that more developed regions, such as North America, have relatively low cancer mortality rates despite having high cancer incidence. On the other hand, some less developed regions, such as Africa, had relatively high cancer mortality despite having low cancer incidence, due to varying technological access (Chen et al., 2020). It is essential to recognize the need for more effective cancer treatment options, as the issue becomes more pressing.

In the US, cancer death rates have decreased nationwide. However, data supports a slower reduction of mortality rates in rural areas (1.0% a year) than in urban areas (1.6% a year). (CDC, 2024) This difference can be accounted for by prevention, diagnosis, and treatment opportunities. Common treatment options include chemotherapy, surgery, and radiation therapy, however, immunotherapy, targeted therapy, or hormone therapy have recently become

more popular. (Gersten, 2023) However, new stromal cell-targeting treatments are still needed as there are varied success rates and treatment plans are long and vigorous.

In Texas, nearly 148,000 Texans are expected to be diagnosed with cancer in 2024, according to the American Cancer Society. More than 23,000 of Texas' projected diagnoses are expected to be for female breast cancer, nearly 21,000 for prostate cancer, and about 14,500 for lung and bronchus cancer. There has been an increase in cancer in younger Americans, while a decrease in cases in patients 65 years and older (Reed, 2024).

Overall, despite advancements in cancer treatment, effectiveness remains a struggle, as traditional treatments fail to consider the tumor stroma in targeting strategies. Future research should focus on developing accessible treatments targeting these stromal cells, as global economic inequalities may hinder the availability of new technology. While the response to cancer therapy has improved in the US, mortality rates due to cancer have overall increased globally. In this study, I will introduce the role of the tumor stroma in treating cancer, as well as upcoming technology to help with treatment.

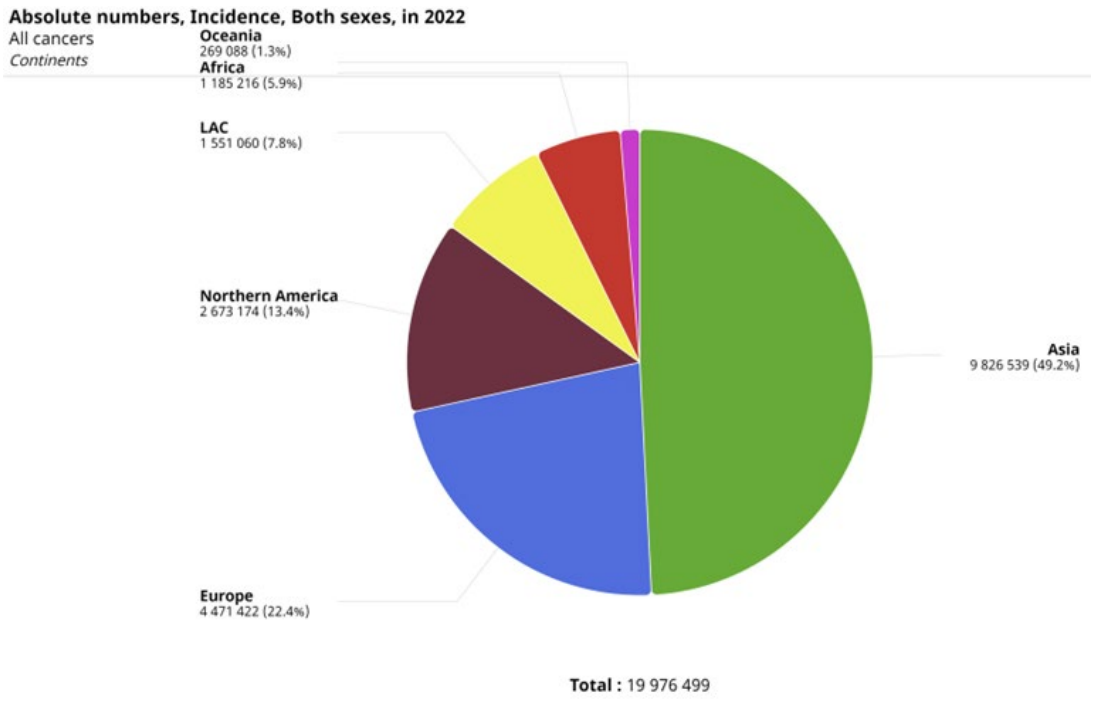

Figure 1. Cancer incidences by continents in 2022. (Created by T Kadiri using data from Cancer Facts & Figures 2023)

Methodology

This research paper aims to analyze the role of tumor stroma in cancer treatment. The research was conducted by reviewing various credible scientific journals and articles. Previous articles about standard cancer therapies and how the stroma affects resistance were analyzed. In addition, multiple studies were analyzed for the use of stroma-targeting strategies with traditional cancer therapies. The growing field of nanomedicine was taken into account, as well as its potential for involvement in cancer therapy administration. Specific studies examining the effects of different nanoparticles in combination with cancer drugs were considered. No physical data was collected, primarily relying on online studies. The potential for bias was eliminated by using various studies from different authors to consider multiple perspectives.

Standard Therapies for Cancer

Discrete modalities evolving from conventional methods, such as surgery, chemotherapy, and radiotherapy, towards more personalized and precise therapies, including such as immunotherapy, hormonal therapy, and targeted therapy, have been used to treat various cancers. For targeted therapy, different inhibitors of specific biomarkers or signaling pathway molecules such as MMPs have been or are being tested preclinically and clinically due to their crucial roles in cancer progression and chemoresistance (Tune et al., 2022).

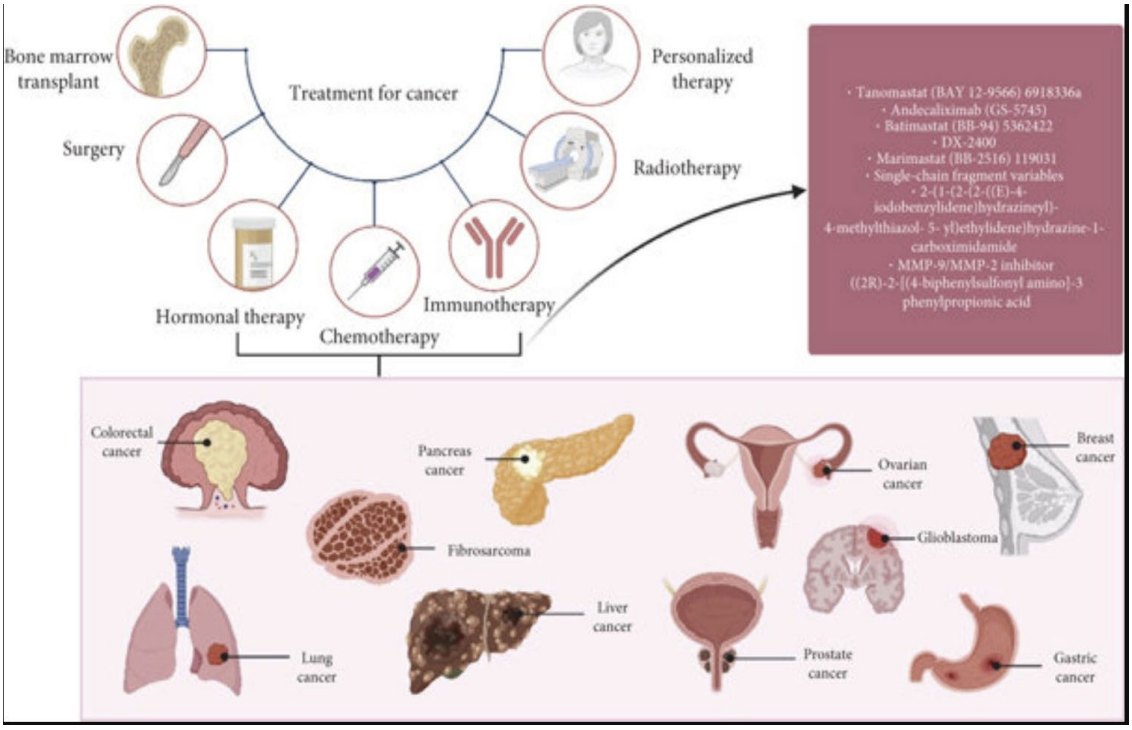

Figure 2. Various Treatments for Cancer. Source: Tune et al., 2022 Description: Common treatments for cancer include bone marrow transplants, surgery, hormonal therapy, chemotherapy, immunotherapy, radiotherapy, and personalized therapy.

Chemotherapy is used to both treat cancer and ease its symptoms. When used with other treatments, chemotherapy can make a tumor smaller, destroy remaining cancer cells, help other treatments work better, or kill cancer cells that have returned or spread. However, chemotherapy not only kills cancerous cells, but also healthy cells, causing symptoms like mouth sores, nausea, and hair loss. How you feel depends on the type of chemotherapy you are getting, the dosage, the type of cancer, how advanced the cancer is, and how healthy you are before treatment. Chemotherapy can be administered orally, intravenously, by injection, intrathecally, intraperitoneally, intra-arterially, or topically. However, the treatment is most often administered through an IV, a needle placed in your vein (National Cancer Institute, 2023).

Radiation therapy uses high levels of radiation to kill cancer cells and shrink tumors by damaging their DNA. Cancer cells with damaged DNA stop dividing and die. They are then able to be removed from the body. However, radiation therapy takes days or weeks to kill the cells, with cells continuing to die even after the treatment is halted. There are two main types of radiation therapy: external beam and internal. Factors considered when choosing your treatment include the type of cancer, size of the tumor, tumor location, medical history, and age. External beam radiation therapy is administered locally, directly aiming at the location of the cancer. It is administered by a loud machine

that moves around you, sending radiation from multiple locations. Internal radiation therapy is also a local therapy, however, the radiation is placed inside your body as a liquid (systemic therapy) or solid (brachytherapy) (National Cancer Institute, 2019).

Immunotherapy helps the immune system detect and destroy cancer cells, reducing tumor growth. The different types of immunotherapy include Immune checkpoint inhibitors, T-cell transfer therapy, Monoclonal antibodies, treatment vaccines, and immune system modulators. Immune checkpoint modulators block immune checkpoints, which normally keep immune responses from being too strong. T-cell transfer therapy enables your T-cells to fight cancer more effectively. Immune cells are taken from the tumor sign, and a sample of the strongest is selected or developed in a lab. These cells are then injected back into your body. Monoclonal antibodies are used to mark cancer cells so they are better seen and destroyed by the immune system. These antibodies are created in a lab to bind to targets on cancer cells. Finally, treatment vaccines and immune system modulators enhance the body's immune system response to cancer (National Cancer Institute, 2019).

Hyperthermia is a type of cancer treatment in which body tissue is heated to high temperatures to damage and kill cancer cells while not harming healthy tissue. However, treatment is not widely available and has only been administered to the following cancers: appendix cancer, bladder, brain cancer, breast, cervical cancer, esophageal cancer, head and neck cancer, liver, lung cancer, melanoma, mesothelioma, sarcoma, rectal cancer. Different techniques to administer the technique are radio waves, lasers, ultrasounds, heating fluids to put in the body, and heated chambers. External hypothermia treats tumors on or below the skin. Doctors place heating devices around the site. Endocavitary hyperthermia is used to treat tumors near or within body cavities by inserting heat into the tumor. Deep tumors are treated with interstitial hyperthermia. While under anesthesia, the patient will have probes or needles inserted into the tumor to transfer the heat source inside the site. Unfortunately, hypothermia is not easily accessible, leading to the treatment being less available in clinics. In addition, it is not proven that the treatment makes patients live longer (National Cancer Institute, 2021).

Surgery, when used to treat cancer, is a procedure in which a surgeon treats cancer by using scalpels, and other sharp tools to cut through skin, muscles, and sometimes bone assisted with anesthesia, during surgery. After surgery, these cuts can be painful and take some time to heal. Apart from involving cuts with scalpels, surgery can also be performed by Cryosurgery or cryotherapy treatment in which extreme cold produced by liquid nitrogen or argon gas is used to destroy abnormal tissue. Another type of treatment is with Lasers, in which surgeons use powerful beams of light to cut through tissue. This technique is primarily used for detailed surgeries. Lasers can also be used to shrink or destroy tumors or growths that might turn into cancer (National Cancer Institute, 2015).

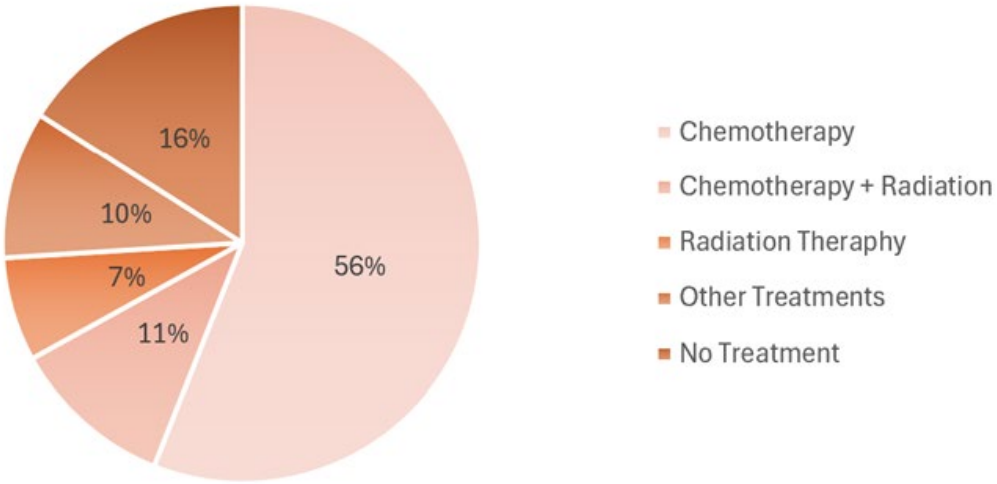

Figure 3. Percentage of Cancer Patients Undergoing Various Treatments. (Created by T Kadiri using data from Cancer treatment and survivorship statistics 2022)

Resistance to Therapy

Traditional cancer treatments often slow down or reverse the treatment of cancer, leading to unwanted results. One example is cytotoxic chemotherapy, which targets rapidly proliferating cells. Chemotherapy is not 100% successful due to the intervention of the stroma. The cells may resort to autophagy, rather than apoptosis, allowing the non-cancerous stromal to survive and adapt to the treatment. The cells change their behavior from one causing cell death to one causing a non-lethal effect, resulting in the tumor growing (Valkenburg et al., 2018).

Radiation therapy holds similar effects, resulting in fibrosis (thickening and scarring of tissue). This reaction leads to an increase in stromal cells and extracellular matrix (ECM), both of which support the survival and resistance of cancer cells. After radiation exposure, fibroblasts show increased expression of integrins, which are proteins that help cells attach to their surroundings. In pancreatic cancer, for example, the fibroblasts upregulate the B1 integrin, protecting the pancreatic cancer cells from radiation therapy. Fibroblasts exposed to radiation may also cause cells to become resistant to therapy. In pancreatic cells, irradiated fibroblasts increased HGF/ MET signaling in nearby cancer cells, increasing their reach and potential (Valkenburg et al., 2018).

Similarly, targeted therapies may prove unsuccessful, as they target one gene or pathway. Because cancers are heterogeneous, targeting one protein or pathway may cause another to be upregulated, letting the cancer survive. A study analyzed the effects of Bevacizumab, an antibody that targets VEGFA (protein involved in blood vessel formation), on mice with lung cancer. The results showed that the bevacizumab led to resistance by upregulating several proteins (VEGFA, FGF2, FGFR2, PDGFRA) in stromal cells (Valkenburg et al., 2018).

While the primary goal of immunotherapy is to trigger an immune response to cancer cells, the extracellular matrix (ECM) may obstruct this function. For example, the ECM protein tenascin can prevent immune cells from entering the tumor. In a study conducted on mice, those without tenascin showed increased immune cell infiltration than the wild-type mice. In addition, the molecular organization of the ECM may hold a key role in the passage of effector immune cells through the stroma. For example, activated T cells were more abundant in the loser, fibronectin, and collagen regions of the ECM, than the denser regions. There is also a direct correlation between blood vessel count and the abundance of T and B cells in tumor tissues. Essentially, denser blood vessels relate to better immune cell distribution (Valkenburg et al., 2018).

The Tumor Microenvironment (TME)

The tumor microenvironment (TME) plays a pivotal role in the growth and treatment of tumor cells. In a tumor's early stages, a relationship forms between the cancer cells and the surrounding tumor microenvironment. This relationship supports cancer cell survival and spread. For example, as tumors grow, they often face a lack of oxygen and a surplus of acidity. In response, the TME promotes angiogenesis (formation of blood cells), which supplies oxygen and nutrients to the tumor, and removes waste products. The TME may also contain immune cells that both support and attack the tumors (Anderson and Simon, 2021).

Immune cells are an essential component of the TME. They may have two roles: suppressing tumor growth and promoting tumor growth. These cells typically fall into two categories: adaptive and innate immune cells. Adaptive immune cells are activated by specific antigens, and have memory, allowing them to respond to threats. One type, T cells, are responsible for attacking antigens. B cells produce antibodies against antigens and natural killer cells kill abnormal cells. Innate immune cells are non-specific. For example, macrophages digest pathogens and dead cells. Neutrophils respond to infections and Dendritic cells provide antigens to T cells to initiate a response. The TME can be categorized based on immune cell presence. Immune infiltrate tumors have immune cells throughout, often during

an immune response. Immune-excluded tumors only have T cells present around the tumor's edges. Finally, immune silent tumors simply lack immune cell activity. (Anderson and Simon, 2021)

Fibroblasts play a critical role in communication between cancer cells and the TME. Typically, when tissue is injured, fibroblasts are transformed into myofibroblasts, which are involved in wound healing. Through TGF-B signaling, these cells exhibit proliferation, ECM formation, and secrete phenotypes. As tumors are never healing, these fibroblasts are continuously stimulated. (Anderson and Simon, 2021)

Macrophages ingest and digest pathogens, present antigens to T cells, and help with healing tissue. Categorized based on function, M1 macrophages are involved in killing cells, typically associated with an anti-tumor response. M2 macrophages are involved with wound healing and have immunosuppressive properties, which may promote tumor growth. In the TME, the M2 macrophage is typically promoted due to the lack of oxygen and presence of cytokines. These cells are often found surrounding blood vessels within the TME. They secrete vascular endothelial growth factor, which leads to angiogenesis. This process essentially leads to tumor growth (Anderson and Simon, 2021).

Neutrophils are a type of white blood cell that may either suppress or promote tumor growth. In the tumor's early stages, neutrophils promote inflammation by releasing cytokines and reactive oxygen species. However, as the tumor progresses, the neutrophils start to promote tumor growth by modifying the extracellular matrix, releasing VEGR, and producing MMP-9 (Anderson and Simon, 2021).

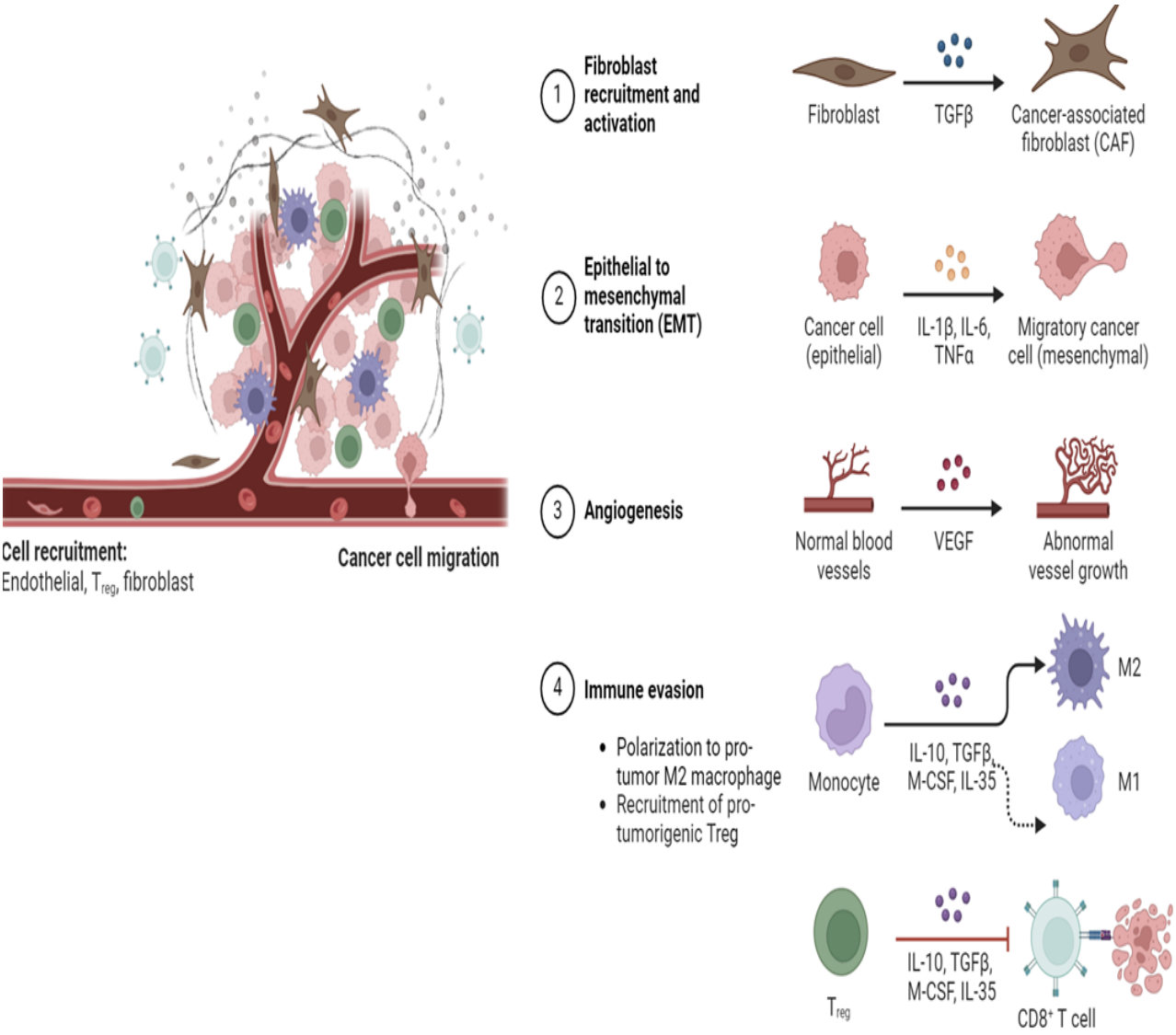

Figure 4. The Tumor Microenvironment. (Created with BioRender.com) The supportive stroma is constructed by recruiting and activating fibroblasts. The EMT allows cancer cells to migrate. Angiogenesis provides the tumor with vital nutrients to continue growing. Immune evasion allows the cancer cells to escape the immune system.

Nanomedicine for Targeting the Stroma

The tumor stroma has been proven to significantly impact the effectiveness of cancer therapies, often aiding in tumor growth. However, in recent years, there has been more research conducted in the use of nanomedicine to help in the delivery of drugs in the tumor, specifically targeting the stroma. To target signaling pathways associated with the ECM, nanoparticles were created using proteins, lipids, and polymers, encapsulating chemotherapeutic drugs. Some of these devices that have been approved include Abraxane, Genexol-PM, Caelyx, and Onivyde. Research has shown that nanoparticles composed of inorganic materials (gold, silver, silica) have the potential to implement photodynamic and photothermal therapy. Furthermore, nano-delivery systems now allow cellular toxins, radioisotopes, and chemo-therapeutic agents to be better targeted without harm to healthy cells. However, this method relies on accumulation in

the tumor and has only demonstrated limited success. Future research targets regulating the TME to improve drug delivery (Su, 2023).

Table 1. Pre-Clinical Studies for Cancer using Nanoparticles (Kadiri, 2024).

Type of therapy	Type of Tumor	Target	Compounds/Function	Nanoparticle	Animal Model
Chemotherapy Combination	Triple-negative Breast Cancer	TGF-B	Tranilast (TGF-B inhibitor), Doxorubicin, Doxil	Organic (polymeric micelles)	PANC-1-luc/NIH3T3 orthotopic nude mice
Gene Therapy	Pancreatic	TGF-B	Fraxinellone (TGF-B inhibitor), Mutant KRAS siRNAs	Organic (polymeric NPs and lipoprotein NPs)	Panc-1/NIH3T3 orthotopic pancreatic tumor-bearing nude mice
Chemotherapy Combination	Pancreatic	Stromal Matrix	Gemcitabine, Metformin (PSC activation inhibitor)	Inorganic (iron oxide NPs)	Panc-1/PSC subcutaneous and Panc-1-luci/PSC orthotopic pancreatic tumor-bearing BALB/c nude mice

Ongoing Clinical Studies Targeting Tumor Stromal Components

In these studies, we can determine the effects of CD40 inhibitors on cancer treatment, in combination with other therapies. CD-40 targeting therapies help the cancer-immunity cycle by promoting tumor-specific T-cells and reprogramming the tumor microenvironment. Therefore, the tumor is reduced. The Results in Table 2 below are ongoing studies and are awaited.

Table 2. Clinical Studies with CD-40 inhibitors for cancer therapy (Kadiri, 2024).

NCI Study Number	Type of Tumor	Type of Stromal Component	Type of Treatment	Combination
NCT04491084	Lung Cancer	monocytes	Anti-CD40 Antibody	Radiation Therapy, FLT3 Ligand
NCT04337931	Melanoma	monocytes	CD40 Agonistic Antibody	stereotactic body radiation therapy
NCT04059588	Melanoma	monocytes	Anti-CD40 Antibody	2141-V11
NCT02225002	Solid Tumors	monocytes	CD40-specific agonist monoclonal antibody	CP-870,893
NCT06205849	Pancreas Cancer	monocytes	CD40 Antibody	Mitazalimab, Surgical IRE

Conclusion

In conclusion, stromal components play a pivotal role in tumor progression and resistance to therapy. Therefore, it is essential to consider the impact of stromal components when administering cancer therapy.. Common cancer treatment techniques, such as chemotherapy or radiation therapy, are often unsuccessful because of factors from the tumor microenvironment. The use of nanomedicine to regulate the stroma sounds promising, however, more research must be conducted. In addition, the technique currently relies on accumulation and currently demonstrates limited success. There is research being conducted on the use of strategies to reprogram the TME using molecules/antibodies targeting specific signaling pathways, such as CD40. These strategies would be used in combination with traditional cancer therapies, to increase effectiveness. By prioritizing further study into bypassing the impact of the stroma on cancer treatment, we can immensely lessen cancer mortality rates.

Limitations

The study reports current trends. These results are fundamentally subject to changes in medical situations. Ethical standards and patient privacy rules have restricted the scope of cases and data from the patients that can be involved in the study, which can impact the applicability of the research findings in the real world. For future research, the researcher plans to account for further available literature, especially those considering the monocytes. Although several studies have been conducted on monocytes, the researcher was only able to review five of these research papers. Expanding in this area will provide a more detailed understanding of their role in cancer progression. In addition, the researcher would investigate more pathways that specifically target stromal components, as they are showing increasing potential in increasing the effectiveness of existing cancer treatments.

Acknowledgment

I would like to recognize Dr. Prahlad Parajuli, Professor Virgel Torremocha, and Coach Jothsna Ketar, who have proven essential in the process of completing this research paper. They have worked tirelessly giving me important insights, support, and guidance. Dr. Parajuli served as an important role model for me, as his proficiency in Oncology, and Dr. Virgel's classes on literature and proficiency in research writing were essential in writing this paper. Coach Jo, I am very grateful for you offering such a valuable opportunity to high schoolers; I immensely value the lessons I've learned. I would also like to thank my parents and my sister for their help, patience, and encouragement while writing my research paper. Their encouragement and guidance have been invaluable and I could not have done it without them.

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