Kaylee Wang
Havergal College, Sun Life Gene Academic Program (SLAP) in Cancer Biology and Immunology, Toronto, On, Canada Grade 11 March 31,2024

Cytokines and Cancer

Abstract

This paper explores the multifaceted role of cytokines in cancer biology, focusing on their crucial roles in tumor initiation, progression, metastasis, immune regulation, and therapeutic responses. Cytokine are small proteins that help modulate immune responses and inflammation, influencing cancer (disease characterized by uncontrolled cell growth). There are many types of cytokines that are studied for potential cancer treatment such as interleukins and interferons. While some cytokines do enhance immune responses against tumors, others aid tumor growth and metastasis, making their role in cancer therapy very complex. This paper will also discuss the structure of cytokines and their receptors, as well as the risks associated with cytokine-based cancer treatments. Risks include systemic toxicity, immunosuppression, inflammation, and resistance mechanisms. While cytokines do show promise in their role in cancer biology, excessive cytokine signaling can lead to dangerous effects like cytokine storm and tumor immune evasion. Despite these potential risks, research on cytokines offers hope for advancing treatment options for cancer. Ultimately, manipulating cytokine signaling pathways could modulate the tumor microenvironment and introduce us to more effective therapies.

Keywords: Cytokine; Tumor initiation; tumor progression; tumor metastasis; tumor microenvironment

Cancer is a term familiar to many, and rightfully so, its mention can evoke fear in some individuals. Cancer is a complex disease characterized by uncontrolled cell growth and proliferation, often influenced by the surrounding microenvironment. This disease can start almost anywhere in the human body, which is made up of trillions of cells[(1)]. Normally, human cells go through a process called cell decision to form new cells as the body requires; when old cells become damaged, they die and new cells take their place. However, this orderly process does break down sometimes, and abnormal or damaged cells grow and multiply when they shouldn't, forming tumors which can be cancerous. These cancerous tumors invade nearby tissues and can travel to different places in the body to form more tumors (metastasis).

Cytokines are small proteins that play crucial roles in controlling the growth and activity of other immune system cells and blood cells. When they are released, they signal the immune system to do its job and increase the body's efficiency in modulating immune responses, inflammation, and tissue homeostasis. Cytokines impact the growth of all of the body cells that help immune and inflammation responses. Most importantly, they help to boost anti-cancer activity by sending signals that can help make abnormal cells die and normal cells live longer, impact tumor progression, metastasis, and therapeutic responses[(2)]. Cytokines are made by many cell populations, but they are mainly produced by helper T cells (Th) and macrophages. They may be produced in and by the peripheral nerve tissue during physiological and pathological processes by macrophages, mast cells, endothelial cells, and Schwann cells[(3)]Some cytokines are produced in a lab and specifically used to treat cancer, or to help prevent and manage chemotherapy side effects. One specific type of cytokine is called a chemokine, which makes immune cells move toward a "target". There are many different kinds of chemokines, including interleukins and interferons, which can be injected under the skin into a muscle or a vein [(2)].

Interleukins are a group of cytokines that act as chemical signals between white blood cells. More specifically, Interleukin-2 (IL-2) increases the speed of which immune system cells grow and divide. An approved man-made version of IL-2 exists and is used to treat advanced kidney cancer and metastatic melanoma, and can be used as a single drug treatment or be combined with

chemotherapy and other cytokines like interferon-alfa. IL-7, IL-12, and IL-21 are other interleukins that are continuously studied for use against cancers like breast cancer, both as adjuvants or stand-alone agents [2] .

Interferons (IFN) are chemicals that help the body resist cancers and virus infections, and those that exist are IFN-alfa, IFN-beta, and IFN-gamma. Only IFN-alfa is used to treat cancer as it enhances the ability of certain immune cells to attack cancer cells, and slows the growth of cancer cells and the blood vessels tumors need to grow. IFN-alfa can be used to treat many different cancers such as: hairy cell leukemia, chronic myelogenous leukemia (CML), follicular non-Hodgkin lymphoma, and more. Unfortunately, there are many severe side effects that may make interferon treatment not usable for everyone due to different tolerance levels. Most side effects also tend to be long term, and rare long-term effects include nerve damage in the brain and spinal cord.

There is an intricate network of cytokines that drive the process of tumor growth and initiation, both of which are dynamic processes driven by the complex interplay of genetic alterations, environmental factors, and interactions within the tumor microenvironment. Tumor necrosis factor -alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 (IL-1) and pro-inflammatory cytokines, which are often elevated in the tumor microenvironment promotes tumor initiation and progression. They are produced predominantly by activated macrophages and are involved in the up-regulation of inflammatory reactions, creating a pro-tumorigenic atmosphere that supports aberrant cell growth and survival [3].TNF-α, also known as cachetin, is an inflammatory cytokine that plays a pivotal role in some pain models as it acts on several different signaling pathways through two cell surface receptors, TNFR1 and TNFR2 to regulate apoptotic pathways, NF-kB activation of inflammation, and activate stress-activated protein kinases (SAPKs). They are also present in neurons and glia, and have been proven to play key roles in both inflammatory and neuropathic hyperalgesia[3].TNF-α also stimulates the production of reactive oxygen species (ROS) and DNA-damaging agents, contributing to genetic instability and facilitating tumor initiation. Additionally, TNF-α promotes cell proliferation by activating NF-κB and MAPK signaling pathways, which regulate the expression of cell cycle progression genes and anti-apoptotic pathways. The pro-inflammatory cytokine Interleukin-6 (IL-6) is another that plays a crucial role in the tumor microenvironment, which is found to be deregulated in cancer when found at high concentrations. Its prominence has been reported in almost all types of tumors. The strong association between inflammation and cancer is shown through the high levels of IL-6 in the tumor microenvironment where it promotes tumorigenesis by regulating all hallmarks of cancer and multiple signaling pathways like apoptosis, survival, proliferation, angiogenesis, invasiveness, metastasis, and the metabolism [7].

Cytokines also play a crucial role during critical stages in cancer development like tumor progression and metastasis, which are marked by the dissemination of cancer cells from the primary tumor site to distant organs, leading to secondary tumors being formed. Cytokines play pivotal roles by being a key regulator in various cellular and molecular events within the tumor microenvironment. During the process in which a tumor progresses, cytokines contribute to the acquisition of metastatic properties by promoting epithelial-mesenchymal transition, which is a phenotype that enables cancer cells to detach and invade surrounding tissues. Additionally, cytokines such as TGF-β, VEGF, and IL-8 stimulate angiogenesis, which is the formation of new blood vessels, which is essential for providing nutrients and oxygen for tumor growth and facilitating the dissemination of cancer cells to distant tissues and organs. Cytokines also play an

important role in establishing pre-metastatic niches, which are specialized microenvironments that promote the growth of metastatic cancer cells. Interactions that are facilitated by cytokines between cancer cells and stromal cells within pre-metastatic niches creates an advantageous environment marked by immune suppression and the attraction of pro-metastatic immune cells. This promotes the proliferation of metastatic cancer cells. As a whole, cytokines have multifaceted effects on tumor progression and metastasis, which continuously proves its high potential as therapeutic targets for inhibiting cancer spread.

Although cytokines have shown promise in cancer therapy by modulating immune responses and inhibiting tumor growth, there are many risks that come along with it. The several factors that contribute to potential risks associated with cytokine-based cancer therapy are systemic toxicity, immunosuppression, inflammation, tumor suppression, and resistance mechanisms. Cytokines can have pleiotropic effects on various cells and tissues throughout the human body. A systemic administration of cytokines may lead to flu-like symptoms, fatigue, fever, and gastrointestinal issues. High doses of certain cytokines like IL-2 and IFN-α can cause even more severe side effects like organ dysfunction, autoimmune reactions, capillary leak syndrome, and death. While cytokines play essential roles in activating immune responses against tumors, excessive cytokine signaling otherwise known as “cytokine storm” can lead to immunosuppression. Hypercytokinemia is the medical term for cytokine storm as it refers to the overproduction of cytokines. When the body loses control of its cytokine production, their excessive numbers cause an internal response that resembles many different diseases [(5)]. Cytokines such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β) have immunosuppressive properties that can inhibit anti-tumor immune responses and instead promote tumor immune evasion. For this reason, cytokine-based immunotherapy’s effectiveness can be compromised due to certain cytokines’ immunosuppressive effect. Pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) can cause inflammatory responses when administered at high doses or over-produced. These inflammatory responses may exacerbate pre-existing conditions or contribute to developing cytokine release syndrome (CRS). CRS is an acute systemic inflammatory syndrome characterized by fever and organ dysfunction. It is associated with chimeric antigen receptor (CAR)-T cell therapy and therapeutic antibodies[(5)]. Some cytokines have been implicated paradoxically in promoting tumor growth and progression under certain conditions. For instance, interleukin-6 (IL-6) and interleukin-8 (IL-8) have been shown to enhance tumor cell proliferation, survival, and invasiveness in certain cancer types. If these cytokines are to be administered as part of cancer therapy, it may inadvertently stimulate tumor growth and metastasis. Finally, resistance mechanisms may be developed if one experiences a prolonged exposure to cytokine-based therapies. Tumor cells may upregulate expression of cytokine receptors and simultaneously downregulate signaling pathways downstream of cytokine receptors. They may also secrete counter-regulatory cytokines to evade the effects of cytokine therapy. This resistance mechanism will limit the effectiveness of cytokine-based cancer treatments and cause for alternative therapeutic strategies to arise.

In summary, cytokines play a multifaceted role on health and diseases, particularly focusing on their implications in cancer biology. As a whole, cytokines serve as crucial players in immune responses, inflammation, and tissue homeostasis, exerting diverse effects on various cell types throughout the human body. In the context of cancer however, cytokines play pivotal roles in tumor initiation, progression, metastasis, immune regulation, and therapeutic responses. With

our ability to modulate cytokine signaling pathways, it is possible to manipulate the tumor microenvironment and develop new strategies for cancer treatment. Unfortunately, cytokine-based therapies don't come without its fair share of potential risks such as systemic toxicity, immunosuppression, inflammation, tumor suppression, and resistance mechanisms. Ultimately, further research on cytokine biology holds promise for advancing treatment options, and guides the development of effective treatment options in the fight against cancer.

References

1.*What Is Cancer? - NCI*. (2021, October 11). National Cancer Institute. Retrieved March 12, 2024, from https://www.cancer.gov/about-cancer/understanding/what-is-cancer
2. *Cytokines and Their Side Effects*. (2019, December 27). American Cancer Society. Retrieved March 12, 2024, from https://www.cancer.org/cancer/managing-cancer/treatment-types/immunotherapy/cytokines.html

3.Zhang JM, An J. Cytokines, inflammation, and pain. Int Anesthesiol Clin. 2007 Spring;45(2):27-37. doi: 10.1097/AIA.0b013e318034194e. PMID: 17426506; PMCID: PMC2785020.https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2785020/

4.Wang X, Lupardus P, Laporte SL, Garcia KC. Structural biology of shared cytokine receptors. Annu Rev Immunol. 2009;27:29-60. doi: 10.1146/annurev.immunol.24.021605.090616. PMID: 18817510; PMCID: PMC3981547. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3981547/

5.Hickman, R. J. (2023, June 6). *Cytokine Storm: Symptoms, Causes, Diagnosis, Treatment*. Verywell Health. Retrieved March 17, 2024, from https://www.verywellhealth.com/cytokine-storm-syndrome-4842383

6.Metcalfe RD, Putoczki TL, Griffin MDW. Structural Understanding of Interleukin 6 Family Cytokine Signaling and Targeted Therapies: Focus on Interleukin 11. Front Immunol. 2020 Jul 16;11:1424. doi: 10.3389/fimmu.2020.01424. PMID: 32765502; PMCID: PMC7378365. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7378365/

7.Lan T, Chen L, Wei X. Inflammatory Cytokines in Cancer: Comprehensive Understanding and Clinical Progress in Gene Therapy. Cells. 2021 Jan 8;10(1):100. doi: 10.3390/cells10010100. PMID: 33429846; PMCID: PMC7827947.

https://www.nature.com/subjects/cytokines
https://www.uptodate.com/contents/cytokine-release-syndrome-crs