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Cancer Plays Hide and Seek Game with Immune System

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Abstract

Cancer is a dreadful disease responsible for taking millions of lives from all over the world every year. Disturbance during the cell cycle results in the abnormal growth of the tissues in the body. Body's immune system is expected to identify these abnormal cells and kill them though cancer cells have been observed to weaken the immune system on many occasions. Development of immunotherapy to treat cancer is a breakthrough to bypass the side effects of the other treatment modalities available now, since immune cells also has the capability to identify and kill cancer cells. Biological drugs include antibodies, vaccines and non-specific immunotherapy such as Interferon and interleukins are available fall under this category. But cancer cells have their own hide and seek game to escape from the eyes of the immune system. Cancer cells evade immune cells by producing several immune suppressive cytokines checkpoints to inactivate the immune cells or change their local environment, so it becomes a hostile place for immune cells to work. Possible mechanisms operated by the cancer cells to evade from immune system are discussed.

Keywords: Immunotherapy; cancer escaping from immune cells; possible mechanisms by cancer cells

Introduction

Cancer is a disease in which the body's normal control mechanism stops and abnormal cells divide uncontrollably. Old cells do not die and instead grow out of control, forming new, abnormal cells. These extra cells may form a mass of tissue, called a tumour which in turn destroys body's healthy tissues by encroaching nearby tissues. Cancer cells can also spread to other parts of the body through the blood and lymphatic systems. Many patients are treated for cancer, and spent rest of their life, and die of other causes. Many others are treated for cancer and still die from it, although treatment may give them more time: even years or decades. Millions of human lives are lost due to cancer every year and possible causal factors responsible for the development of the disease are identified such as overexposure to light due to modern lifestyle [1- 4], synthetic chemicals [5] and some virus and microorganisms [6]. The list increases in length every year due to the focus by the scientist to save mankind from this dreadful disease.

Chemotherapy and radiation therapy are the two most common types of cancer treatment. They destroy these fast-growing cells including other types of fast-growing healthy cells [such as blood, sperm and hair root cells], causing adverse reactions, or side effects. The immune system also helps to fight cancer. Many new methods of treatment based on immunology were evolved. Some of those became a sort of "game changers'' in cancer therapy. The immune system

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is an in built protection system from illness and infection that reacts and gives responses to “non self” in the body, for example, damaged cells or infections. Some immune cells can recognise cancer cells as well as abnormal cells and kill them and so immune system is important to patients who suffer with cancer though this may not be enough to get rid of a cancer altogether. Different types of immunotherapy adopt different strategies. Some immunotherapy treatments help the immune system stop or slow the growth of cancer cells. Others help the immune system to destroy cancer cells or stop the cancer from spreading to other parts of the body. Immunotherapy treatments can be used alone or combined with other cancer treatments. Nevertheless, cancer is also "Smart" and capable of escaping immune system that can fight cancers.

Understanding Immune System

Two different types of the immune system operate in our body. One that works from birth [in built immune protection, innate immunity] and the second what we develop after having certain diseases [acquired immunity].

Innate immunity

The innate immunity is always ready and prepared to defend the body from infection immediately. This inbuilt protection system comes from a barrier formed by the skin around the body, the inner linings of the gut and lungs, which produce mucus and trap invading bacteria, hairs that move the mucus and trapped bacteria out of the lungs, stomach acid which kills bacteria, helpful bacteria growing in the bowel, which prevent other bacteria from taking over, urine flow which flushes bacteria out of the bladder and urethra, white blood cells called neutrophils, which can identify and kill bacteria. Many factors can overcome and damage these natural protection mechanisms. For example: something may break the skin barrier, such as having a drip in the arm or a wound from surgery, a catheter into your bladder can become a route for bacteria to get inside the bladder and cause infection antacid medicines for heart burn may neutralise the stomach acid that kills bacteria.

Adaptive Immunity

Adaptive immunity is a defence mechanism which our body builds when it meets and remembers the antigens [another name for germs and other foreign substances] in the body. Antibodies are produced to fight against the antigens though 14 days are needed for our body to make specific antibodies. More importantly, the body memorizes this fight so that if its meets the same antigen again, it can recognize and attack more quickly. Antibody production is one of the most important ways to develop immunity. There are two types of adaptive immunity:

1.Active Immunity - antibodies that develop in a person's own immune system after the body is exposed to an antigen through a disease or when we get an immunization [i.e. a flu shot]. This type of immunity lasts for a long time.

2. Passive Immunity - antibodies given to a person to prevent disease or to treat disease after the body is exposed to an antigen. Passive immunity is given from mother to child through the placenta before birth and through breast milk after birth. It can also be given medically through blood products that contain antibodies, such as immune-globulins. This type of immunity is fast acting but lasts only a few weeks or months.

Vaccines provide active immunity to the disease. Vaccines do not make sick, but they can trick our body into believing to have a disease, so it can fight the disease.

Here is how a vaccination works:

1. The vaccine is administered antigens to a specific disease.

2. The immune system identifies the antigens in the vaccine as foreign invaders.

3. The immune system then develops antibodies to neutralize the antigens.

The immune system stores these antibodies for future use in case the person is ever exposed to the disease. Vaccines are given to prevent and eventually wipe out diseases. When a vaccine is given to a significant portion of the population, it protects those who receive the vaccine as well as those who cannot receive the vaccine. This concept is called "herd immunity." When a high percentage of the population is vaccinated and immune to a disease, they do not get sick and so there is no one to spread the disease to others. This herd immunity protects the unvaccinated population from contagious [spread from person to person] diseases for which there are a vaccine [7; 8].

Cancer may weaken immunity

Cancer can weaken the immune system by spreading into the bone marrow that makes blood cells to fight infection. This happens most often in leukaemia or lymphoma, but it can happen with other cancers too. The cancer can stop the bone marrow from making so many blood cells. Certain cancer treatments can temporarily weaken the immune system by a drop in the number of white blood cells from bone marrow. Cancer treatments that are more likely to weaken the immune system are:

- chemotherapy
- targeted cancer drugs
- radiotherapy

•high dose of steroids

Highlights of Cancer Immunotherapy

In the recent past cancer immunotherapy is an innovative treatment in vogue for cancer treatment [9-11]. Immune system efficiently fights off cancer or pre-cancer conditions on a regular basis without even bringing it to our notice. The types of immunotherapy include:

*immune checkpoint inhibitors [ICIs],

*cellular immunotherapy,

*exosome immunotherapy [12].

These therapies create an immune microenvironment and modulate intestinal microbiota and tumour gene mutation. By employing these therapies drug resistance and adverse drug reactions are avoided. However, there is still a lot of scope to reduce side effects and improve the targeting of the therapy [13]. Unlike chemotherapy, which targets directly on cancerous tumours, immunotherapy treats patients by acting on their immune system. Immunotherapy can boost the immune response in the body as well as teach the immune system how to identify and destroy cancer cells [14]. Fewer side effects are observed than other treatments, because it targets just the immune system and not all the cells in the body so cancer may be less likely to return. The immune system can clearly recognize cancer cells as different, yet often it is unable to stop them from growing. Scientists have made a breakthrough in the development novel potential drugs that can kill cancer cells. They have discovered a method of synthesizing organic compounds that are four times more fatal to cancer cells and leave non-cancerous cells unharmed. Their research can assist in the creation of new anticancer drugs with minimal side effects. In the laboratory scientists can produce different chemicals that are part of the immune response. Monoclonal antibodies and tumour-agnostic treatments are by administering:

•Checkpoint inhibitors

•oncolytic virus therapy

•T-cell therapy

•cancer vaccines

The immune system fights with cancer

The immune system consists of a complex process to make “biological” which are used in the prevention, diagnosis, or treatment of cancer and other diseases. Biological drugs include antibodies, vaccines and non-specific immunotherapy such as Interferon and interleukins [15; 16].This process involves the organs, cells and proteins. Monoclonal antibodies are made in a laboratory to boost your body’s natural antibodies or act as antibodies themselves. Monoclonal antibodies can help fight cancer in different ways. For example, they can be used to block the activity of abnormal proteins in cancer cells. This is also known as a targeted therapy, or cancer treatment that targets a cancer’s specific genes, proteins, or the tissue environment that helps the tumour to grow and survive. Other types of monoclonal antibodies boost your immune system by inhibiting or stopping immune checkpoints. An immune checkpoint is normally used by the body to naturally stop the immune system’s response and prevent it from attacking healthy cells.

Cancers escaping the immune system

Cancer cells can find ways to hide from the immune system by activating the checkpoints [17]. The cytotoxic T-lymphocyte–associated antigen 4 [CTLA-4] and programmed death 1 [18] immune checkpoints are negative regulators of T-cell immune function. The cancer cells that have reached the “escape” stage no longer possess the molecules that show any danger. The B cells and phagocytes then fail to recognize them as a result the T cells are not activated and the cancer cells are not destroyed. Marasco and colleagues have discovered a key protein that is needed to activate this escape process [19,20].

During depth study to find out the failure of suppressor genes to destroy cancer cells, Stephen Elledge team identified more than 100 mutated tumour suppressor genes: genes that regulate cells during cell division and replication. The mutated genes can prevent the immune system from spotting and destroying malignant cells in mouse models. This observation challenges the conventional idea that the majority of mutations in tumour suppressor genes cause cells to divide and grow uncontrollably. More over this behaviour of the immune system doesn't do more to fight early-stage tumours [21]. Stephen Elledge said that "The shock was that these genes are all about getting around the immune system, as opposed to simply saying 'grow, grow, grow!" Immune cells recognize danger through a group of molecules found on the surface of all cells in the body [22]. This helps them inspect potential problems closely and decide whether to attack. The 'cancer immune-editing phase' or the "Escape phase" in which tumours can evade immune by producing several immune suppressive cytokines, either by the cancer cells or by the non-cancerous cells present in the tumour microenvironment [23]. The molecules that would otherwise reveal the cancer to the immune system are lost, and killer T cells move past, unaware of the danger the cancer cell could cause. “Cancer cells also develop ways to inactivate immune cells by producing molecules that make them stop working.” They also change their local

environment, so it becomes a hostile place for immune cells to work [24; 25]. Tumour cells that evade detection can be explained by the following proposed mechanisms: down regulation of major histocompatibility class [MHC] I expression - allowing antigen to go unrecognised. The main reason the human body is unable to fight cancer is because it cannot differentiate between patient's own DNA and cancer cell DNA and so taken for granted as its own [26]. A new mouse study by researchers at the Francis Crick Institute uncovered a protein that aids tumours evade the immune system. It's exciting to find a previously unknown mechanism for how our body recognizes and tackles tumours. This opens new avenues for developing drugs that increase the number of patients with different types of cancer who might benefit from innovative immune-therapies [27]. The scientists also identified gasoline, a protein that is present in blood plasma secreted by cancer cells, and the mechanism of interfering with the immune system's defences by blocking a receptor inside dendritic cells. Clinical data and samples from cancer patients with 10 different types of the disease were analyzed, and the researchers observed that individuals with liver, head and neck, and stomach cancers, who have lower levels of this protein in their tumours had higher chances of survival [28].

Chronic inflammation is a critical hallmark of cancer, with at least 25% of cancers associated with it, and possible underlying causes include microbial infections, autoimmunity, and immune deregulation [29;30].Whether or not inflammation is a cause or a consequence, the tumour microenvironment [TME] is compromised, triggering an immune inflammatory response, and histopathological analyses provide evidence for the presence of innate and adaptive immune cells in most human tumours, which are characterized as features of cancer progression [31]. It is currently accepted that an aberrant innate and adaptive immune response contributes to tumorigenesis by selecting aggressive clones, inducing immune suppression, and stimulating cancer cell proliferation and metastasis [32]. During the early stages of tumour development, cytotoxic immune cells such as natural killer [NK] and CD8+ T cells recognize and eliminate the more immunogenic cancer cells [33]. This first phase of elimination selects the proliferation of cancer cell variants that are less immunogenic and therefore invisible to immune detection. As the neoplastic tissue evolves to a clinically detectable tumour, different subsets of inflammatory cells impact tumour fate. For example, high levels of tumour-infiltrated T cells correlate with good prognosis in many solid cancers [34 -36].

on the other hand, high levels of macrophage infiltration correlate with a worse prognosis [37-39]. Involvement of macrophages has been described in every step of cancer progression, from early neoplastic transformation throughout metastatic progression to therapy resistance [40 - 42]. During carcinogenesis, anti-tumour macrophages display an M1-like polarization that plays a relevant role in the elimination of more immunogenic cancer cells. As the tumour progresses, the TME elicits an M2-like polarization of Tumour-associated macrophages [TAMs] that is protumorigenic [43]. TAMs promote tumour progression in different ways, such as stimulating angiogenesis and lymphangiogenesis, stimulating both cancer cell proliferation and epithelial–mesenchymal transition, limiting the efficacy of therapies, remodeling the extracellular matrix [ECM], promoting metastasis, and inducing immunosuppression of anti-tumour effector immune cells [44;45;39]. TAMs also directly stimulate cancer cell proliferation through the secretion of epidermal growth factor [EGF] [46], promote tumour angiogenesis by vascular endothelial growth factor [VEGF] secretion [47], and remodel the ECM by secreting metalloproteinases [MMPs] [48]. Although TAMs mostly play protumorigenic roles, they can also sometimes exert anti-tumoral roles. Additionally, TAMs mediate the efficacy of the anti-tumor and anti-metastatic effects of the histone deacetylase inhibitor TMP195, which reprograms TAMs to a highly phagocytic phenotype [49]. Similar to the M1/M2 phenotype of macrophages, it has been proposed that tumour-associated neutrophils [TANs] which exist in two polarization states, called "N1" and "N2," to describe protumor and anti-tumour populations, respectively [50]. Cancer cells exploit the immunosuppressive properties of T cells while impairing the effect or functions of anti-tumor T cells, such as their ability to infiltrate tumours and their survival, proliferation, and cytotoxicity [51]. The antigen-dependent nature of the effector T cells implies that the effectiveness of the anti-tumour T-cell immune response depends on both the ability of the tumour antigen to induce an immune response [immunogenic] and the presence or absence—of inhibitory signals that can impair the T cells' functions [52]. Accordingly, it is widely accepted that, in a T-cell-dependent process, most neoplastic cells expressing highly immunogenic antigens will be recognized and killed during the early stages of tumour development [53].

The less immunogenic cancer cells escape the immune control of T cells and survive, a process termed cancer immune editing [34]. The final outcome is that the surviving cancer cells adopt an immune-resistant phenotype. In parallel, during tumor development, cancer cells evolve mechanisms that mimic peripheral tolerance and are able to prevent the local cytotoxic response of effector T cells as well as those of other cells, such as TAMs, NK cells, and TANs [33].

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