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Review Article

Cancer Survives Against All Odds

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Abstract:

Human body constantly replace old and non-functional cells with new cells, during this process cells carrying damaged DNA is not repaired or die can develop cancer. The converted cells overrule all control mechanisms set for normal cells. Cancer cells can evade the immune system by mimicking peripheral immune tolerance. As a result of 'cancer immune-editing phase' or the "Escape phase" tumours can evade immune system by producing several immune suppressive chemokines and cytokines and other members of the families. Impact of genetics on the development of cancer is explained with childhood cancer since they have not been exposed to mutagens before the development of the disease.

Key words: cancer; escape phase; immune tolerance; chemokines, immunotherapy

Introduction

Those who are born (living beings), have every right to live, whether they are beneficial or not to mankind? Obviously, if they are harmful, man wants to eliminate them. Cancer is one of those but "smart" enough to survive.

From a single cell (zygote) entire fully functional human body is formed by repeated cell divisions and differentiation. After birth, our bodies are constantly replacing old and non-functional cells with newly produced cells, among these newly produced cells some of which have the potential to become cancerous even at childhood stage. Childhood cancers are almost always caused by a DNA mutation. Most cancers in children are thought to develop as a result of mutations in genes that lead to uncontrolled cell growth and eventually cancer. Children with acquired DNA mutations can't pass them on to their children in the future [1, 2]. To begin with, we don't have cancer cells in our bodies [3]. At any given moment, we may be producing cells that have damaged DNA, most of the times; cells with damaged DNA either repair themselves or die off through apoptosis. During this constant production of new cells, some of which have the potential to become cancerous only when neither of those things happens [2].

Genetics play a crucial role in the prognosis of cancer, since it is interesting to observe that each cancer has a unique combination of genetic changes. During further growth of the cancer additional changes also may occur. Even within the same tumour, different cells may have different genetic changes. Mutations which are the causal factor for cancer in one context may not be the same in another contest, is a great puzzle in cancer study. Now, using zebra fish and human pleuripotent stem cell cancer models, research shows that not all cells with genetic mutations become cancerous. The specific combination of factors is likely to be different in each type of tumour [4].

It was an enigma thirty years ago for the scientist to offer a coherent answer to the question that why our own cells turn out to be hostile by becoming cancerous inside our system. Though uncontrolled proliferation of cells could be triggered due to many factors such as chemicals, radiation, and viruses was known. Exact mechanism as how it happened was a mystery [5]. Researchers tried to solve the mysteries and found that cancer cells overcome cell regulatory system. Such as:

1. DNA repair system: This system operates in virtually every cell in the body, detecting and correcting errors in DNA. Across a lifetime, a person's genes are under constant attack, both by carcinogens imported from the environment and by chemicals produced in the cell itself. Errors also occur during DNA replication. In most cases, such errors are rapidly corrected by the cell's DNA repair system [6].

2. Apoptosis: The prevention of cancer is one of the main functions of apoptosis typically, it is the intrinsic pathway that is inhibited in cancer, and there are a wide range of means to inhibit apoptosis. The loss of apoptotic control allows cancer cells to survive longer and gives more time for the accumulation of mutations which can increase invasiveness during tumour progression, stimulate angiogenesis, deregulate cell proliferation and interfere with differentiation [7,8]. Cancer cells can ignore the signals that tell them to self-destruct. So they don't undergo apoptosis when they should.

3. Limits of cell division: The body cells cannot reproduce endlessly. Once the telomeres are shorter than a threshold length, they trigger an internal signal that causes the cell to stop dividing. If the cells continue dividing, further shortening of the telomeres eventually causes the chromosomes to break apart or fuse with one another, a genetic crisis that is inevitably fatal to the cell.

Cancer cells overrule all the 3 cell regulatory systems. Unlike normal cells, cancer cells can proliferate indefinitely. Scientists have recently discovered the molecular basis for this characteristic—an enzyme called telomerase that systematically replaces telomeric segments that are trimmed away during each round of cell division. Telomerase is virtually absent from most mature cells, but is present in most cancer cells, where its action enables the cells to proliferate endlessly. In cancer cell DNA aberrations are never corrected. Further cancer cells never undergo apoptosis; however at certain stage they undergo necrosis.

More epidemiological evidence

The early epidemiological studies suggested that the origin or causes of cancer may lie outside the body and more important, that cancer could be linked to identifiable and even preventable causes as we described in the book "Darkside of the night light" [9]. These ideas led to a widespread search for agents that might cause cancer. By the mid-1970s, scientists had started to develop the basis of our modern molecular understanding of cancer. In particular, Ames and others established the relationship between mutagenicity and carcinogenicity formed a strong basis to support for the idea that chemical carcinogens has the power to damage cellular genes there by providing a model for the initiation of cancer [10]. Carcinogens induce mutations in critical genes, and these mutations direct the cell in which they occur, as well as all of its progeny cells, to grow abnormally resulting years as a tumour. The inheritance of some tumours sometimes appears to run in families. If cancer is caused by mutations in critical genes, then people who inherit such mutations would be more susceptible to cancer's development than people who do not have.

Evidence from Childhood Cancers

A term used to describe cancers that occur between birth and 14 years of age. Childhood cancers are very rare and may differ from adult cancers in the way they grow and spread, how they are treated, and how they respond to treatment. Childhood cancers tend to occur at different sites from those common in adults. Perhaps the biggest divergence is that cancer is far more common in adults than children, largely because the genetic mutations that spur the disease can take years to accumulate and affect cell growth and division. The average age at diagnosis is 8 overall (ages 0 to 19), 5 years old for children (aged 0 to 14), and 17 years old for adolescents (aged 15 to 19). Among children (ages 0 to 14 years), the most common types of cancer are leukemias, followed by brain and other central nervous system tumours, lymphomas, neuroblastoma, kidney tumours, and malignant bone tumours Among the most common childhood cancers are leukemias, lymphomas, brain tumours, and bone cancer[1]. Each of these cancers also occurs in adults, but adult cancers are more likely to strike the lung, colon, breast, prostate, and pancreas. Inherited versus acquires gene mutations. Some children inherit DNA changes (mutations) from a parent that increase their risk of certain types of cancer. These changes are present in every cell of the child's body, and they can often be tested for in the DNA of blood cells or other body cells.

Cancer can evade the immune system to Survive

The body's defence mechanism offers protection and in some cases, helps in destroying cancer cells. It is surprising to observe that in some occasion's tumours have been known to disappear spontaneously, in the absence of any targeted treatment, usually after an infection (bacterial, viral, fungal or even protozoa). Constant battle between good and evil goes on inside your body as long as life is persisting. The antagonism between inflammation and immunity also affects the outcome of cancer treatment and needs to be considered when designing new therapeutic approaches [11].

A complicated immune mechanism is encountered when it comes to cancer. Cancer cells evolve different mechanisms that mimic peripheral immune tolerance in order to avoid tumoricidal attack.

Two main strategies are operated to escape immune attack by the cancer cells. Tumour cells avoid immune recognition and instigate an immunosuppressive the tumour microenvironment (TME). In the first, cancer cells may lose the expression of tumour antigens on the cell surface, thus avoiding the recognition by cytotoxic T cells.

In the second, cancer cell-derived factors instigate an immune-tolerant TME by secretion of suppressive molecules, expression of inhibitory checkpoint molecules and induction of the recruitment of TAMs, MDSCs, and Tregs by tumour-derived chemokines such as, CCL2, CSF1, CCL5, CCL22, CXCL5, CXCL8, and CXCL12 (12-15).The cumulative effect of all these strategies result in a complex and efficient system for immune evasion [11]. As cancer cells display unique characteristics in comparison to normal cells, researchers can take advantage of these differences when coming up with ways to combat cancer [16].

Immune cells recognize danger through a group of molecules found on the surface of all cells in the body [17]. This helps them inspect potential problems closely and decide whether to attack. But when a cancer reaches the 'escape phase' it can change. 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. 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 [18]. 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 [19,20].

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 recognize it. This is because cancer cells consist of the patient's own DNA, which the body's immune system recognizes as natural [21]. 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 [22]. Scientists identified secreted gasoline, a protein that is present in blood plasma and is also secreted by cancer cells, and discovered how it interferes 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 [23].

Immunotherapy as a Treatment Modality

Cancers have evaded immune system to avoid for their survival hence scientist have thought if cancers can be brought back under the control of immune system that can be the best cancer management modality. The unique characteristics of the cancer cells are very helpful in involving immune system for treatment of some types of cancer. Immune cells can recognize cancer cells since they are abnormal and kill them. In the laboratory scientists can produce different chemicals that are part of the immune response. So, they can make different types of immunotherapy such as: monoclonal antibodies (MABs), which recognise and attack certain proteins on the surface of cancer cells

- vaccines to help the immune system to recognise and attack cancer
- cytokines to help to boost the immune system
- CAR T-cell therapy (also called adoptive cell transfer) to change the genes in a person's white blood cells

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